

No Foreign Aid Without Tears

ALTHOUGH the third United Nations Conference on Trade and Development, which opened last week at Santiago, Chile, has begun as rancorously as had been expected, there have been some welcome surprises. The opening speech by the President of Chile, Mr Salvador Allende, was not the anodyne welcome which the delegates to UNCTAD III might well have looked for, but rather a fierce declaration that the developed countries of the world are dragging their feet on foreign aid. Mr Robert McNamara, the president of the World Bank, supported this argument with a gloomy assessment of the likelihood that the industrialized nations of the world would attain by the end of the 1970s the modest target of spending 0.7 per cent of their Gross National Product on foreign aid—the prospects are that the richest of them all, the United States, will move in the other direction and that by 1975 only 0.24 per cent of its GNP will be allocated to official foreign aid. But Mr McNamara also complained that the developing countries are too often pursuing domestic policies which accentuate the present inequalities between the rich and the poor—his specific complaints about Brazil and Mexico will remove him from a good many Christmas card lists. This week, Dr Sicco Mansholt, the new president of the Commission of the European Communities, has reinforced earlier complaints that the developed nations are not doing enough for the developing world and has declared that the industrialized countries must somehow liberalize their trading relations with developing countries so as to increase their imports of manufactured goods from what is called (for obscure reasons) the Third World. By contrast, the delegates of advanced communities, Britain and the United States included, have cut an overcautious figure. Why must the United States Administration so persistently offer Congress as an excuse for not doing more? Why should the United Kingdom insist, as it does, that private investment in developing countries, valuable though it may be, is a sufficient excuse for not toeing the line that 0.7 per cent of a country's GNP should be spent on foreign aid without commercial strings attached? The truth is that many of the most urgent needs in developing societies are for public investment in social institutions in education and public health, and that strictly commercial investment usually serves to provide jobs in manufacturing industry, a quite separate objective.

If the pattern of previous UNCTADs (in 1964 in Geneva and in 1968 in Delhi) is repeated in Santiago, the formal speechmaking will drag on throughout next week and even the one after, and only then will the hard bargaining begin. In the past few years, there has been some welcome progress in the abolition of tariffs on manufactured products from the developing world and by now the countries in the European Communities, the Scandinavian countries, the United Kingdom, Japan, the Soviet Union, Czechoslovakia and Hungary have implemented a version of the scheme originally put forward by Mr

Edward Heath in 1964 that manufactured imports from developing countries should have a special preference of this kind. Yet there is too much evidence that advanced countries will implement such schemes only when they are not themselves inconvenienced. Quantitative restrictions on imports of such things as textiles are clapped on whenever a domestic industry appears to be in trouble. And the United States still shelters behind the obscurantism of Congress, with its parochial concern for domestic industry. But is there any reason why advanced societies should not adopt a uniform and a much more liberal policy on tariffs and other quantitative restrictions? Is there any reason why they should not extend this liberalization of trade to agricultural products? And would it not be sensible if they were to acknowledge that the monetary device of Special Drawing Rights at the International Monetary Fund—"paper gold" as they have been called—should be made available to developing countries and, preferentially, to those developed countries who are generous with their foreign aid? There is at least a chance that this device would be complicated enough to bamboozle Congress and thus allow the United States to play a more creditable part in foreign aid.

Quarrels at Santiago have an interesting and important connexion with the speculations which there have been in developed countries in the past few months about the undesirability of economic growth. Some, like Dr Barry Commoner, argue that continued economic growth in countries such as the United States will bring intolerable pollution. Others, like the authors of the study at MIT which was sponsored by the Club of Rome (see *Nature*, 236, 47; 1972), assert that economic growth is likely, for similar reasons, to have to be limited in the world at large, and, even though they argue to their credit that foreign aid should be increased, they assert (in the face of all the evidence) that economic growth in developed nations serves merely to increase the gap between the rich and the poor. In the past few weeks, Dr Mansholt himself has been arguing that the industrialized nations of Western Europe would have to limit their economic horizons. The difficulty, of course, is that these gloomy predictions are likely, whatever the inclinations of their authors, to limit the capacity of the industrialized nations to spend as much as they should on foreign aid. The United Nations is hoping that in the 1970s the Gross National Product of the developing world will grow at an average of 6 per cent per annum, from which it can be calculated that the developing countries will have to increase their imports by 7 per cent a year and that they will have to finance this either by an increase of exports of 7.5 per cent a year or by a corresponding increase of their debt to the industrialized communities. It is inconceivable that this can be done without sustained economic growth in the developed world. Moreover, it is plain that the target is too modest. If the economic growth of the developed world is merely 6 per cent a year throughout the 1970s, this will correspond merely to an



increase of 3.5 per cent a year in GNP per head in the developing world—not nearly enough to make a substantial difference to the present unequal distribution of prosperity. If the world is to be within sight of an equitable balance between rich and poor countries by the end of the century, the real growth of prosperity in the developing world should be the equivalent of more like 10 per cent than 6 per cent a year, and at the beginning at least, this will have to be financed by increased production in the industrialized nations of the world. In short, there is a danger that too much alarm about the distant but speculative limits to economic growth may serve, whatever its authors intend, as an intolerable brake on the process of social development in the countries where the need is greatest.

European Technology

ON the face of things, the conference being held this week at Venice by the Commission of the European Communities is unlikely to do as much as its sponsors hope for the fuller exploitation of technology in Europe. A part of the trouble is that the conference will mix together discussions of the ways in which technology might be more fully exploited with discussions of less tangible questions, regional policy, one of the Communities' perennial hot potatoes, and the still more fashionable preoccupations with multinational enterprises—are they benefits or millstones round the neck of the European enterprise? To be sure, the organizers are right in thinking, as apparently they do, that it is not feasible to divorce technological development from a consideration of the structure of industry, but on this occasion they have put the cart before the horse and have decided to spend more time than is necessary at this stage on long-term problems which are essentially political in character and too little on the structural questions which are of practical and immediate importance. It is all very well, for example, to brood about the policy for regional development which the Communities should pursue, and Mr Derek Ezra, the chairman of the National Coal Board, will no doubt be eloquent on the subject. Yet it remains an open question whether at this stage the Communities should commit themselves to a policy that will inhibit the further growth of industry in parts of Europe already industrialized for the sake of encouraging industry to move to regions which are still comparatively rural. To be sure, there are important social problems to be dealt with, but there is at least a chance that the Communities' concern with environmental matters (also on the agenda at Venice) might be more adequately met by concentration, not dispersion.

The missing elements in the conference agenda suggest that a valuable opportunity is being lost. So far, the Communities have sought to increase the pace of technological development by devices such as the removal of technical barriers to trade and the introduction of a European patent system and, indeed, there is no doubt that the creation of the Communities, which allow for free trade and the free movement of capital (in due course), will powerfully stimulate the growth of technologically founded companies of all kinds. Yet under present circumstances, there are no European institutions

for helping to remove the technological chauvinism by means of which European countries set out on needless and wasteful competition with each other. The competitive development of fast reactors in Britain, France, Germany and even Italy is a continuing scandal, unlikely to be tackled at Venice. Is it not time, the sad example of Euratom notwithstanding, that Brussels paid some attention to this question? And is it not high time that steps were taken to channel public investment in the several aircraft industries of Europe into coordinated programmes? The cooperative programmes on computer development, the most tangible products of the Aigrain working groups of 1969, have been a disappointment. And nothing much has yet been done to make the work of large government research establishments—the defence research establishments in Britain, for example—more widely available not merely to European governments but to industrial companies. It would have been valuable if the conference at Venice could have tackled subjects like these. Its preoccupation with the more distant problems seems likely to give it an air of unreality.

Concorde Economics

THE British and French governments have only themselves to thank for the mess they have got themselves into with their plan to develop a supersonic air transport. Last week, Mr John Davies (for Britain) and Mr Jean Chamant (for France) agreed that work should begin in earnest on a further six aircraft, bringing the total to sixteen. In the same breath, they agreed to a further increase of the development budget for this risky venture, which is now quickly approaching £1,000 million. At the same time, like other entrepreneurs before them, the two governments are anxiously confronting the awkward question of whether their new products will be commercially viable. The chances are that in the next few weeks, Air France and British Overseas Airways Corporation will be persuaded by the two governments to confirm at least some of their tentative orders for the Concorde, but this is not a seller's market. Nobody will be surprised if the two national airlines are able to buy their Concorde at bargain prices. If the airlines are sensible, they will not quibble much about the initial cost, likely to work out at a little more than £20 million an aircraft, but will ask for a continuing subsidy on the cost of operation, if only on the grounds that by putting these novel aircraft into service before there is an economically compelling case for doing so, they are helping the manufacturers to demonstrate (if that is possible) that supersonic aircraft are indeed an economic benefit.

That other airlines should lag behind is entirely understandable. After all, potential customers have at present no means of knowing where supersonic aircraft will be allowed to operate. It will be a long time before the American authorities will be prepared seriously to consider applications for permission to fly supersonically over the United States and Canada—questions of critical importance to airlines in North America. And although there is scope for using Concorde on the transatlantic and transpacific routes as well as between Europe and Africa, it remains something of a puzzle to know whether journeys between, say, Frankfurt and New York will be

hampered by the need to fly subsonically over the first part of the journey. Then there are more detailed economic questions to consider. Is there, for example, a chance that supersonic aircraft can be turned round at international airports with the speed that will be necessary if operators are to make, as they must try, the fullest use of their capital investment? Will their use in airline service be anything like as flexible as the manufacturers claim? And what, in any case, will be the economic penalties that will no doubt stem from the applications for certificates of airworthiness that will in due course have to be obtained from agencies such as the Civil Aeronautics Board in the United States?

Another uncertainty, more distant but in principle at least more damaging, is that the effects of commercial operations of supersonic aircraft on the constitution of the stratosphere are still unclear. The notion that the discharge of large quantities of water vapour from supersonic aircraft exhausts might seriously deplete the ozone layer and thus increase the incidence of skin cancer on the ground is no longer regarded as a serious possibility¹. There is more reason to fear the effects of nitrogen oxides. Johnston² has drawn attention to the way in which either NO or NO₂ can act as a catalyst for the destruction of ozone in an environment in which atomic oxygen is available for the reconversion of NO to NO₂ and has gone so far as to calculate that a fleet of 500 supersonic transports operating for an average of seven hours a day might reduce the concentration in the stratosphere by a factor of two or thereabouts. In reality, of course, as the unhappy plight of the British and French governments demonstrates clearly enough, there will be plenty of time for a detailed study of the consequences of nitrogen oxides in the stratosphere before the airlines of the world have such a fleet in operation, and in any case Johnston's calculation has been disputed on the grounds that it makes too much use of equilibrium processes in circumstances where dynamical processes are known to be important and because the sensitivity of the stratosphere to nitrogen oxides is based on the supposition that nitrogen oxides are at present responsible for the whole of the difference between the observed and theoretical concentrations of ozone in the stratosphere. It will be a great surprise if other minor constituents do not turn out to have a similar effect, with the result that nitrogen oxides will be discovered to be less powerful means of catalysing the destruction of ozone than has been supposed. Yet for the airlines, dithering about the purchase of supersonic aircraft, the fear that at some point in the next few years the operation of these aircraft might have to be restricted in order to preserve the important characteristics of the stratosphere is yet another reason for thinking that a decision should best be postponed until more is known about the hazards of commercial operation.

What, in circumstances like these, should the governments of Britain and France attempt to do? With close on £1,000 million committed to the development of Concorde, and with £600 million already spent, it would plainly be unwise to abandon the whole venture and sell for scrap the aircraft now being manufactured. At the same time, it would be prudent to acknowledge that commercial airlines will only reluctantly follow Air France and BOAC in equipping themselves with Concorde. And there is always a danger that both the national airlines

will either be made less profitable than they should be by their involuntary purchase of these aircraft or will, once committed, turn out to be less sensitive than they should be to whatever cautionary lessons may be learned from further study of the stratosphere. So would it not make sense for both governments to agree that the best way of bringing Concorde into service would be to set up yet another international airline, with the single function of operating the fleet of Concorde now being built and provided with opportunities to function as a contractor for the ordinary commercial airlines, not merely Air France and BOAC but such other international carriers as may be interested? To be sure, there would be problems about reciprocity of landing rights, but these are not insuperable. It would also be held that such a governmental airline would tend to make its decisions on political and not commercial grounds but that, of course, is as it should be—whether or not the ordinary commercial airlines adopt the supersonic aircraft, they will in the last resort be responding either to political pressures from the governments of France and Britain or to the commercial pressures which will arise if two out of the international airlines are persuaded against their better judgment to go into the supersonic transport business before the time is ripe. Even at this late stage the sponsoring governments should give this serious consideration.

¹ *Inadvertent Climate Modification*, Report of the Study of Man's Impact on Climate (SMIC) (MIT Press, 1971).

² Johnston, H., *Science*, 173, 517 (1971).

100 Years Ago



Sun-spots and the Vine Crop

As the connection of sun-spots with terrestrial phenomena is now largely occupying the attention of scientific men, the following facts may be of some interest. The years in which the wine crop in Germany was unusually good seem (in this century, at least) to have returned at regular intervals. The close coincidence of these years with the years of minimum sun-spots is shown by the following table:—

Minimum of Sun-spots.	Wine-years.	Minimum of Sun-spots.	Wine-years.
1784·8 ...	1784	1833·8 ...	1834
1798·5 ...	(?)	1844·0 ...	1846
1810·5 ...	1811	1856·2 ...	1857
1823·2 ...	1822	1867·2 ...	1868

I may add that the gentleman who first remarked the regular recurrence of wine-years at intervals of about eleven years was not aware of the periodicity of the sun-spots, and could not therefore have been in any way prejudiced. The years given in the above table are the only ones known in Germany as good wine-years.

These facts agree with the results of Messrs. Piazzi Smyth and Stone, who found that the mean temperature on the surface of the earth was subjected to a period of eleven years.

ARTHUR SCHUSTER

Owens College, Manchester, April 23

From Nature, 5, 501, April 25, 1872.

OLD WORLD

Policy in Doubt

A CORRECT balance between pure and applied research cannot be achieved merely by calling upon Lord Rothschild, according to the Prime Minister. Mr Heath was addressing the Parliamentary and Scientific Committee on Monday and he added that an essential ingredient for achieving this correct balance is the "will, the intention and the expectation of doing better".

Mr Heath also doubted the wisdom of having a national science policy. He feared that such a policy "would have to be described in terms so general as to make its value doubtful". In this Mr Heath was preempting the Select Committee on Science and Technology which in the past few months has set out to discover among other things whether a national science policy is really needed. The committee's report, which is imminent, will possibly pronounce on this issue, although the scientists from whom evidence was taken were, in general, undecided on whether or not Britain should have such a policy.

Necessary generalities in the formulation of a national science policy, said Mr Heath, could be disguised by "high sounding phrases" but he added that this "would not get us anywhere. It would be a sham that would hide the real difficulties that exist". One of the chief difficulties, said Mr Heath, would be to decide how to compare the merits of different types of research but he brightened the day for all advocates of Lord Rothschild's thinking by adding that in these circumstances it is the "user or his representative . . . [who] is best able to take decisions about the need for research—and how much research on each subject".

Mr Heath affirmed his faith in pure research, which he said had the very important function of increasing and rejuvenating the nation's scientific capital. This capital consists not only of new knowledge, said Mr Heath, but it also includes the "scientists, engineers and the mathematicians who in the future will continue the job of creating new knowledge".

Mr Heath also promised continuing support for the training of postgraduate students. He said that the government was determined that the creators of new scientific capital shall be available in the numbers required. All the same, Mr Heath warned that it was important not to have too many qualified scientists, engineers and mathematicians and that the numbers must be kept under continuous review.

Amongst the optimism, Mr Heath

issued a word of warning. He said that the government is faced with the problem of how best to use its limited resources and that it has to view the competing claims of different research subjects—in particular "the perspectives of health, of poverty, of education—in which, of course, science and research have a crucial role". The

government has to view these problems "not as subjects isolated from each other but as part of an integrated effort to make our country a better place to live in".

"Science and scientific research", concluded Mr Heath, "must continue to be harnessed to the task of fulfilling our national need".

ENVIRONMENT

Confidence and Optimism

FROM holography to the salvation of mankind seems to be the chosen route of the 1971 Nobel Laureate in physics, Professor Dennis Gabor of Imperial College, University of London and CBS Laboratories, Stamford, Connecticut.

In the eighth annual Science Policy Foundation lecture delivered on Wednesday, Professor Gabor talked of the new responsibilities of science which, as it turned out, meant yet another contribution to the great environmental debate.

Professor Gabor insisted that he was not prophesying doom; rather he was prophesying a "healthier, happier, less neurotic world"—provided the public and "holders of power take heed of our warnings". In the same breath, however, he declared that unless population growth was stopped and the rate of depletion of the Earth's resources reduced, then "we are riding for a fall". To illustrate the problem, Professor Gabor quoted liberally from the much discussed computer calculations published recently in *The Limits to Growth* (Meadows D. H., et al., Universe Books, New York and London, 1972). Professor Gabor calls these calculations "the great controversy: Forrester and Meadows *versus* the rest". Professors Jay Forrester and Dennis Meadows are the colleagues at MIT who have pioneered computer predictions of world dynamics. The calculations in essence show that unless radical changes are instituted in our way of life, then a major pollution crisis will be upon us in seventy years.

Professor Gabor, is not a blind believer in computer calculations; but people who reject computer calculations out of hand remind him of the Dominicans who refused to look into Galileo's telescope. While admitting that there are many shortcomings in the calculations as they stand, he considered that there is one unavoidable conclusion: "if we want to avoid a

catastrophe in not more than one, or at most two, hundred years, technology must take a new turn". Such changes will also have to be accompanied by appropriate social reforms, according to Professor Gabor, which must go hand in hand with the changes in technology.

Professor Gabor chided people who advocate complete abstinence from using the Earth's natural resources and said further that there is no need to look for inexhaustible sources of power. He pointed out that the known resources of uranium for fission are virtually inexhaustible provided we are prepared to "grind down granite mountains with less than 0.03 per cent uranium content".

Gabor also dismissed the bogey of heat pollution which has been raised by some ecologists but he admitted that there was no easy answer to the pollution created by cars. In this case he argued for a compromise with motor cars limited to 50 horse power and a high tax imposed on the use of internal combustion engines within city boundaries.

Whereas Professor Gabor expressed optimism about solving the short term pollution problems, he confessed that the long term problems—the depletion of natural resources for example—posed many problems for science and technology. Every effort must be made to recycle waste, low grade mineral ores must be mined and substitutes for limited natural resources must be made of replaceable and inexhaustible raw materials. Further, Professor Gabor said, the lessons learnt from using indestructible plastics are all too fresh in the mind and plastics developed in future must be biodegradable.

Professor Gabor's reasoned survey of environmental problems ended with an expression of confidence that the problems can be solved, although he did add that "my hopes are founded on optimism rather than on solid data". "Optimism" however, said Professor Gabor is "the only working hypothesis for any responsible man".

ENGINEERING

Space Structures

THE official opening last week of the new space structures laboratory at the University of Surrey was a gala occasion attended by some 300 guests of the university. The building, constructed according to a new technique by the British Steel Corporation's tubes division, is a gift from the corporation to the university. Lord Robens, the university's vice-chancellor, said most appropriately, when he accepted the building from Lord Layton of the BSC, that the gift "forged close links" between university and industry.

The building is 100 feet square and is supported only at its sides. The roof is constructed of steel tubes which range in diameter from 2 inch to 3½ inch, and the novelty of the construction lies in the rapid assembly "nodus" joints which connect the tubes. A spokesman for the BSC estimated that the cost of building a similar type of roof elsewhere would be £0.70 a square foot and that the maximum area of a roof of this type—without any central support—is 40,000 square feet.

The development of structures with such large spans in Britain has arisen to a great extent from the efforts of Professor Z. S. Makowski, head of the department of civil engineering at Surrey. Professor Makowski was the consultant to BOAC on the construction of the Jumbo jet hangar at London Airport, which has a span of 450 feet, and the collaboration between the BSC and the University of Surrey in the construction of the new laboratory arises chiefly from Professor Makowski's interest in space structures.

Mr R. G. Taylor gave the BSC's view of collaboration between university and

industry, and he pleaded for greater communication between the two. He also said that there is a need for a "comprehensive schedule or a single reporting point to which research should be referred or from which subjects [for research] might be selected". Mr Taylor thought that the university should orient itself in a much greater way towards sales—"selling first itself and then the fruits of its labours".

Mr Taylor ended on a highly speculative note, calling on British civil engineers to produce a viable alternative to a channel tunnel. A channel bridge, according to Mr Taylor, could now be built, incorporating unprecedented spans, with only fourteen supports compared with the 114 suggested in one of the earlier plans for such a bridge. A bridge, said Mr Taylor, would be eminently preferable to "two tubes underneath the water" which would only take trains.

SPACE

An Imminent Decision

MR MICHAEL HESELTINE announced this week that the British government is providing £240,000 as extra finance to the European Space Conference to enable it to carry out further exploratory work on the possibility of European collaboration in the post-Apollo programme.

It is expected that the ESC ministers will make up their minds on collaboration with NASA in July and the extra finance will give Mr Heseltine—and the British government—breathing space as well as providing time for the minister to find his feet in his new job.

The American invitation calls on European countries to contribute up to 15 per cent of the cost of the programme, which for Britain could amount to £8

million a year, initially for a five year period. Before July Mr Heseltine and the government have to decide on the future course of British aerospace which has been under review since the Black Arrow programme was cancelled last year. In principle Mr Heseltine now has to decide whether or not Britain is interested in working on the space tug which would be launched by the shuttle and operate in orbit.

The £240,000 grant will mostly be spent with British companies. In particular, the British Aircraft Corporation which has been working on a small government grant in collaboration with North American Rockwell on the structural and avionic aspects of the shuttle, will no doubt get a large slice of the money.

The announcement of the grant will no doubt please NASA, which is very keen to have European collaboration in the programme. The launch of Apollo 16 last Sunday was the penultimate thrash of the dying Apollo programme and after the last Apollo launch in December the programme will grind to a halt with many scientific questions about the moon still unanswered. It is in this light that NASA is turning its attention to the thorny problem of the shuttle.

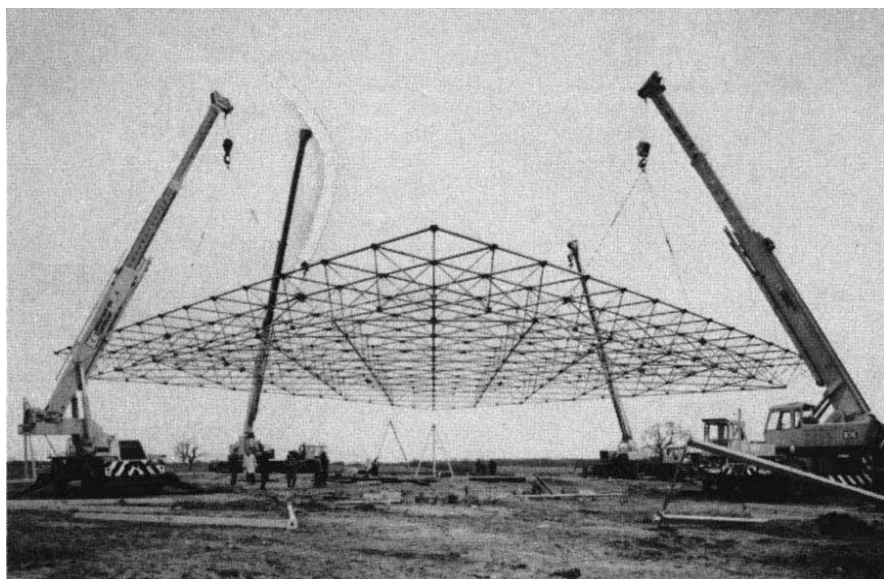
The development of the shuttle—already much curtailed in size and scope compared with the original plans—seems now to be assured. But the role Europe will play in the programme will not be clear until July at the earliest. Mr Heseltine has less than three short months to assess the position.

ENVIRONMENT

Davoll in the Lion's Den

ENGINEERS must realize that ever greater manipulation of the natural world is not intrinsically good and that any problems caused by the application of present technology cannot be "confidently left to the even more potent technology of the future". So ran the thesis of Dr John Davoll, director of the Conservation Society, in an address to a gathering of engineers in London yesterday. Speaking to the somewhat grandiose title "Engineers and the Community Conscience", Dr Davoll acquainted the engineers with the environmental problems which mankind faces today, and pointed them down the road to salvation.

Describing himself as a pessimist ("I believe this is prudent"), Dr Davoll said "we cannot risk the consequences of mistaken optimism". Ridiculing "the sort of calculations, based on exponential growth, that show that in 300 years we shall be standing ten deep on a red hot Earth", Dr Davoll said, however, that "the shorter term calculations are



The roof of the Space Structure Laboratory at the University of Surrey being tested before erection at the BSC's Corby works.

meaningful". These show that unless the developed countries reduce their impact on the environment—by ending economic and population growth—so that the underdeveloped countries can catch up, the developed countries will be "reduced to fighting among themselves for what remains".

But, said Dr Davoll, it is difficult to convince growth-minded economists and technological enthusiasts that the Earth has inescapable environmental limits. "The rarely questioned assumptions of the virtues of technological expansion and a constantly rising Gross National Product emasculate the opposition, and the protests of those who do not regard these things as ends to be pursued, regardless of cost, sound thin and—most damning of all—unrealistic".

Engineers, because they are involved in the planning of projects, can make a significant contribution by looking beyond the short term interests. Quoting the example of the projected breeder reactors which "commits us to problems of radioactive waste disposal . . . for which no known solutions exist", Dr Davoll said that engineers, "like all of us, should ruthlessly question every assumption, and measure it against the problems of our real situation". Engineering and technology can be used, said Dr Davoll, as practical measures to achieve a generally desired aim, a smaller population living within the natural cycles of the Earth. Technology must not be pursued in the mystical belief that whatever can be done should be done.

SCIENCE RESEARCH COUNCIL

"Under Control"

The Science Research Council this week unveiled a film that deals in some detail with one of the specific research fields which the council supports—control engineering. Sir Brian Flowers, chairman of the SRC, says that the film gives an insight into the way in which the council is helping to improve engineering education in universities, and collaboration between academic institutions and industry.

The SRC now funds about twenty control engineering groups at a cost, over the past five years, of about £2 million. Three of these—at the University of Manchester Institute of Science and Technology, the University of Cambridge and Imperial College, London—account for about £1.5 million of this, and are featured prominently in the film.

At Manchester, Professor H. H. Rosenbrock leads a group which has been concerned, for example, with the problem of properly controlling a diesel engine. And Professor J. F. Coales of the University of Cambridge describes in the film the way in which his group has been tackling problems of par-

ticular industrial interest—such as how to control the thickness of paper emerging from a paper mill, and how to optimize the output from an ammonia plant by accurately controlling the physical parameters of the ingoing material. The Department of Computing and Control at Imperial College, headed by Professor J. H. Westcott, has been closely associated with another large scale project involving the control of a cold steel rolling mill at the British Steel Corporation's Abbey Mill in Port Talbot.

Although plans are not yet complete, the SRC says that it will probably produce more films of a similar nature about other fields of research in which it has an interest.

EARTH RESOURCES

Skylarks for All

THE Skylark sounding rocket is Europe's most successful scientific rocket, with nearly 300 successful launches and with only a 13 per cent failure rate. Now, thanks to a suggestion put forward by the Argentine government, a new career for the rocket, as an Earth resources survey vehicle, seems to have been opened up. The first test of Skylark in this capacity was carried out from Woomera on March 27, and details of this flight were released this week.

Two cameras were used in this test, an f24 5½ inch aerial camera and a Hasselblad 70 mm camera; both black-and-white and false-colour photographs of southern Australia were obtained—and recovered—proving the practicality of the system. The emulsions

and filters used were chosen to provide immediate comparison with the Apollo 9 photographs which first demonstrated the value of satellites and rockets for general Earth resources studies. But the extreme flexibility of Skylark—it can carry a variety of payloads—means that any reasonably sized sensor, or up to six cameras, can be accommodated.

Professor R. A. G. Savigear, of the Department of Geography, University of Reading, described the use of sounding rockets from the viewpoint of a potential customer. Because areas of 500,000 km² can be covered on one flight, images of much more uniform quality than those built up from a mosaic of aerial photographs can be obtained; sounding rockets also have advantages over satellites, principally because they can be available just when and where required, and also because the payload is recovered.

Skylark is manufactured by the British Aircraft Corporation, and although it is not yet prepared to quote a price for an Earth resources version, it seems likely that for a complete operation the cost would be roughly similar to that of a scientific mission—of the order of £100,000. This would suggest a cost of £0.10 per km² for a general survey, which is much less than the £1 to £2 per km² required to carry out a similar survey with aircraft.

The resolution which can be obtained depends, of course, on the equipment used. Details 30 m across could be identified in photographs taken from about 200 km (higher, incidentally, than the Gemini orbital missions) but in practice a resolution of about 100 m will probably be sufficient.

HIGHER EDUCATION

More from Abroad

THE number of overseas students in British universities, technical colleges and colleges of education in 1970–71 was 34,564, according to the British Council (*Overseas Students in Britain, Statistical Supplement 1970–71*, £0.10). This is 11 per cent more than in 1969–70.

The Table shows the numbers of students from both Commonwealth and other foreign countries in 1969–70 and 1970–71. Of the 18,338 overseas students who were studying in universities in 1970–71, 5,413 (30 per cent)

were at the University of London, 1,278 at the University of Oxford, and 1,260 at the University of Manchester. Each of the remaining universities had fewer than 1,000 foreign students in 1970–71. But a larger proportion of the 15,712 foreign students in technical colleges—some 51 per cent—attended educational institutions in the London area that year.

The most popular fields of study among students from abroad in British universities are engineering, technology and applied science (4,564); social, administrative and business studies (3,803); and biological and physical sciences (3,271).

Numbers of Overseas Students in Britain (1970–71)

Origin	Universities		Technical colleges	Colleges of education
	Postgraduate	Undergraduate		
Commonwealth countries	5,137 (4,808)	3,843 (3,688)	10,273 (9,769)	417 (428)
Other countries	5,730 (4,991)	3,628 (3,453)	5,439 (4,686)	97 (76)

Numbers in parentheses are for 1969–70.

NEW WORLD

Cleaning up the Great Lakes

by our Washington Correspondent

PRESIDENT NIXON returned from his trip to Canada last week after signing a joint US-Canada agreement to clean up the Great Lakes, and ran headlong into criticism from environmentalists. The treaty, which is the fruit of two years of negotiations, sets standards for the Great Lake waters that are more stringent than those at present prescribed by the Great Lake states, and a rough timescale for meeting them, but it contains no commitment from the United States to remove or limit phosphates in detergents.

Nevertheless, few people have denied the importance of the treaty, which marks the most extensive international agreement on environmental matters yet concluded. Essentially what the treaty does is to pinpoint five objectives for the Great Lake waters—freedom from substances that enter the waters as a result of human activities and settle to form sludge deposits, freedom from floating debris such as oil and scum, freedom from coloration or odour, freedom from materials that are toxic to man or aquatic life and freedom from nutrients that enter the water as a result of human activities in quantities that create “nuisance growths” of aquatic weeds and algae.

Called the Agreement on Great Lakes Water Quality, the treaty updates the International Boundary Waters Treaty signed between the United States and Canada in 1909, and puts more power behind the International Joint Commission—a body consisting of three members each from Canada and the United States which is charged with monitoring the progress of the two nations towards meeting the objectives of the treaty. The commission, which did most of the background work for the treaty, has been given the task of submitting annual reports on progress, and it has also been assigned the responsibility for determining what action is necessary to curb or prevent pollution of Lakes Superior and Huron, which are at present relatively clean.

Specifically, the treaty calls for a reduction in coliform count to 1,000 per litre, a dissolved oxygen level of 6.0 mg per litre in the upper waters of the lakes, total dissolved solids in Lake Ontario and Lake Erie of less than 200 mg per litre, pH in the range 6.7 to 8.5 and radioactivity kept to “the lowest practicable levels”. All the water quality standards should be met at all points in the lake waters, except

for localized mixing areas around sewage outfalls. At present, most of the lakes except for Lake Erie can meet the standards in open waters, but they are now violated in inshore areas.

The treaty has come in for criticism not for its objectives but for the means by which they should be achieved, and for the vagueness of much of the phrasing in the requirements. The treaty calls, for example, for programmes designed to meet the objectives to be “either completed or in process of implementation by December 31, 1975”. That leaves plenty of room for delay, and with the past record of deterioration in water quality, there is a suspicion that the waters are likely to get worse before they will get better.

The treaty also does not commit either government to spending levels, although officials of the Environmental Protection Agency have suggested that it will cost the United States up to \$3,000 million to install the necessary treatment facilities to meet the standards over the next four years. The total will be split between federal and local governments on the one hand and industry on the other, in the rough proportion of \$2,000 million to \$1,000 million, which for the federal government, at least, represents no increase from the present level of about \$400 million a year for treatment facilities in the Great Lakes area.

The treaty has come in for the most criticism in its approach to limiting the levels of phosphates in the lakes. Apart from prescribing the broad objective of reducing phosphates to the level at which they do not produce “nuisance growths” of algae, the agreement commits each nation to the construction of waste treatment facilities to remove phosphorus from municipal wastes, and to the regulations to force industrial

firms to remove phosphorus from their wastes to be discharged into the Great Lakes and their connecting waters. What is missing from the agreement is the commitment to remove phosphates from detergents—the source at present of some 60 per cent of the phosphorus in municipal effluents.

Although few would voice opposition to the plans for constructing treatment facilities for removal of phosphates from sewage, several environmentalists have argued that the condition of Lakes Erie and Ontario is such that more immediate measures are necessary. Since detergents now contribute the major share of phosphates entering the lakes, the argument is that their phosphate content should be limited. Indeed, that is exactly what the Environmental Protection Agency itself was arguing a year ago, and the Canadian government has already set a limit of 5 per cent for the end of this year. But the Administration's policy reversal on phosphate detergents last summer, when Surgeon-General Jesse Steinfeld suggested that housewives should buy phosphate detergents in preference to non-phosphate compositions, set back the movement towards limiting detergent phosphate levels, and the Administration is now putting its money into removal of phosphates from sewage.

The agreement sets out a timetable which would reduce phosphorus input to Lake Erie to half of its present amount, but this would still result in 16,000 tons of phosphate entering the lake in 1976. The agreement itself points out that “available evidence suggests that reductions in phosphorus loadings to achieve a net discharge to Lake Erie in the range 8,000 to 11,000 tons per year may be required to bring about mesotrophic conditions in this lake”.

HIGH ENERGY PHYSICS

PPA Goes Under

THE Princeton Particle Accelerator, which has been living from hand to mouth since the Atomic Energy Commission withdrew financial support for the machine last year, has finally been forced to shut down. The last straw came recently when the National Cancer Institute turned down a grant application which would have provided the accelerator with funds to conduct

cancer research and therapy using heavy ions, and the accelerator was left without operating funds and without any prospect of getting funds in the near future.

Built at a cost of \$40 million, the Princeton Particle Accelerator, which used to be known as the Princeton-Pennsylvania Accelerator, lost support from the Atomic Energy Commission when the AEC's high energy physics budget was being squeezed to accommodate the National Accelerator Laboratory. Since June last year, when

the AEC money ran out, the accelerator has been kept going on a limited scale on money gleaned from foundations and on a few small contracts, and in that time the machine has been altered from a proton accelerator to a heavy ion machine in an attempt to cash in on some of the largest now being devoted to cancer research.

The National Cancer Institute turned down the grant application chiefly on the basis that the Princeton Particle Accelerator lacks sufficient in-house medical expertise to ensure cooperation from the medical community. But Dr Milton White, Director of the PPA, said last week that such a judgment is premature since well-known cancer therapists will not be attracted to the machine until the cancer institute puts up the money to enable it to undertake cancer research. The loss of a grant from the National Cancer Institute also spiked the chances of getting a grant from the National Science Foundation, which had promised to put up some money if the pitch to the cancer institute was successful.

Asked last week what would now become of the machine and its parts, Dr White said that it would be turned off carefully so that it could be revived if funds became available. Otherwise, most of the instruments and magnets are "really just junk" because they are specifically geared to that machine. The nineteen remaining members of staff (the machine had a staff of 350 in its heyday) will also be looking for jobs, although one or two may be slotted into other posts at Princeton.

With the present concentration on cancer research and the much publicized efforts to direct science and technology to solving pressing national problems, the chances of securing money to turn the PPA into a cancer research tool seem good. In the event, however, it has finally become an expensive sacrifice to the 200 GeV machine, which started operation at Batavia recently.

RESEARCH SPENDING

The Numbers Game

by our Washington Correspondent

THE latest contribution of the National Science Foundation to the continuing debate about the relationships between science and the economy was published last week. A set of statistics detailing trends in expenditures on research and development during the past two decades, the report*, according to its introduction, says that for 1972, "moderate R & D growth, shared by all sectors of the economy, is foreseen". Total expenditures on research and development are expected to reach \$28,000

million—an increase of 4 per cent compared with figures for 1971—with federal expenditures on defence and space research and on civilian research set for increases of 2 per cent and 6 per cent respectively.

If inflation is taken into account, however, these increases look distinctly less rosy. Implied in the figures contained in the report, although not made explicit, is that inflation will increase costs by 3 per cent in 1972 so that, in real terms, what the report calls a "moderate increase" boils down to 1 per cent. Moreover, the report shows that research and development are continuing to take a declining share of the Gross National Product—expenditures for 1972 are expected to amount to 2.5 per cent of the estimated GNP, down from 2.6 per cent last year and 3.0 per cent in the heady days of the early 1960s.

As for manpower, the report gives details of the absolute decline in the numbers of scientists and engineers in research and development jobs during the past few years, but makes no predictions for 1972. In 1971, for example, there were 6 per cent fewer jobs available in industrial laboratories than there were in 1970, and 3.5 per cent of scientists and engineers previously employed in research and development were out of work last year. Much of the reason for the decline in employment prospects is, of course, the drop in expenditure on space research since 1968—the report shows that total expenditure on defence and space research declined by 7 per cent between 1968 and 1972 while federal expenditure on civilian research and development has increased by 30 per cent over the past three years.

Among the other statistics included in the report are:

- Expenditure on basic research in the United States is expected to amount to \$4,100 million in 1972—an increase of 2 per cent, or a decline of 1 per cent in real terms.

- Applied research is expected to soak up \$6,400 million this year (5 per cent more than last year), leaving \$17,400 million for development. The trend over the past few years has seen basic research taking a steadily increasing share of the total expenditure on research and development, while the proportion spent on development has been declining.

- Between 1967 and 1969, expenditures on research and development in the United States increased by an average of 5 per cent a year, while in Canada they increased by 9 per cent, in West Germany by 16 per cent and in Japan by 33 per cent.

**National Patterns of R & D Resources*, NSF 72-300, US Government Printing Office, Washington DC 20402; \$0.50.

Short Notes

Branscomb to leave NBS

THE National Bureau of Standards may not be one of the most prominent agencies of the federal government, but its size and influence have been growing steadily during the past few years under the directorship of Dr Lewis M. Branscomb, NBS director since 1969. Last week, however, Dr Branscomb announced that he has accepted a new job as chief scientist for the International Business Machines Corp (IBM), and that he will be leaving the bureau of standards. He had been widely tipped for various federal scientific posts in recent years, including director of the National Science Foundation.

Radiation Standards

THE Supreme Court two weeks ago denied individual states the right to set standards for discharge of radioactive wastes from nuclear power plants that are more stringent than those set by the Atomic Energy Commission. By a vote of five to two, the court denied the State of Minnesota a full hearing on its claim that federal laws which seek uniform standards for radioactive emissions do not necessarily pre-empt the state's own environmental laws.

The court ruling, which was brief and unsigned, was regarded by environmentalists as an important issue because they have often charged in the past that the AEC suffers from a conflict of interest between its regulatory and promotional functions. Environmental groups maintain that the Atomic Energy Commission has in the past been lax in setting standards for discharges, and that the states set more stringent requirements because they have no vested interest in the promotion of nuclear power.

All-share Shuttle

THE decision to use a solid fuelled disposable booster for the proposed space shuttle effectively limits the number of possible launch sites to Cape Kennedy and Vandenberg Air Force Base in California. Last week, the National Aeronautics and Space Administration announced that both have been chosen, thereby confounding speculations that Cape Kennedy would get a monopoly of the shuttle launches, and putting the Department of Defense for the first time in the business of direct operational support of manned space flight. Cape Kennedy will be developed first at an estimated cost of \$150 million, while Vandenberg may not come into operation until the early 1980s. The Department of Defense will bear the costs of converting Vandenberg.

NEWS AND VIEWS

A Better Understanding of Histamine Receptors

THE work of Sir Henry Dale and his colleagues more than fifty years ago showed that the amine histamine, produced by the decarboxylation of histidine, has a variety of powerful biological actions. Histamine is widely distributed in the body, being particularly concentrated in mast cells, and it seems to have important functions in cardiovascular responses to local injury, in immune responses, in the control of intestinal and gastric function and possibly within the central nervous system. A variety of smooth muscles, such as those in the gut and in the bronchi, are stimulated to contract by the application of histamine, and many drugs are known which antagonize these actions. Such drugs have found important clinical uses, particularly in the control of bronchial constrictions, and in the treatment of various allergic responses which result from histamine release.

It has been apparent for some time, however, that more than one type of histamine receptor exists. Certain responses—notably the histamine-induced stimulation of hydrochloric acid secretion by the stomach and also the effects of histamine in increasing heart rate and in inhibiting contractions of the uterus—are not antagonized by the classical antihistaminic drugs, such as mepyramine. It has thus been suggested that these two categories of histamine responses are mediated by different receptors; the H1 (mepyramine blocked) and H2 (mepyramine insensitive) types. The article by Black and his colleagues on page 385 of this issue of *Nature* represents an important advance in understanding the pharmacological properties of these two categories of histamine receptor.

Black and his colleagues report the results of an extensive series of studies of the actions of a wide range of agonists and antagonists on the H1 and H2 histamine responses. Using various different test systems, such as the contractions of isolated guinea-pig intestine (H1), the contractions of rat stomach (H1), the contraction frequency of isolated guinea-pig heart muscle (H2), gastric acid secretion in rat stomach (H2) and electrically induced contractions of rat uterus (H2), the properties of H1 and H2 receptors have been systematically examined.

Black *et al.* found that methyl substituents on the side chain carbons or on the terminal amino nitrogen of histamine had no effect on the relative activity of the resulting compounds on H1 and H2 receptors—the ratio of activities on the two receptors remained similar to those found with histamine itself. Methylation of the histamine ring in positions 1 or 3 yielded compounds which were inactive on both H1 and H2 receptors. But 4-methylhistamine proved to be a selective stimulant for H2 receptors; it retained about 40 per cent of the activity of histamine on such receptors, but had only 0.2 per cent of the activity of histamine when tested in H1 systems. Conversely, the analogue 2-methylhistamine was relatively more active on H1 than on H2 receptors. Pharmacological evidence is produced which suggests that there are true differences in the interactions of these histamine analogues with the different receptors, rather than differences in drug disposition in the various tissues.

An interesting new drug was also discovered by Black

and his colleagues among the substances tested as potential antagonists of the H2 receptors. This compound, burimamide, a thiourea analogue of histamine, seems to be a specific antagonist of the H2 receptors. The drug, for example, blocked the stimulation of gastric acid secretion normally produced by histamine. This blockade was shown to be reversible and competitive, causing a parallel shift to the left in the dose response curves for histamine. The calculated dissociation constant for burimamide was approximately 8 μ M, and this value was similar in the various different H2 receptor systems studied. Burimamide also antagonized H2 responses evoked by various histamine analogues, such as 4-methylhistamine. On the other hand, the drug failed to antagonize H1 responses, unless very high drug concentrations were used, and it also failed to block responses evoked by other pharmacologically active compounds, such as the increase in heart rate produced by isoprenaline by stimulation of β -adrenergic receptors. Burimamide was thus shown to be a selective antagonist of histamine H2 receptors.

Burimamide also seems to be effective in blocking H2 responses in the intact animal. It effectively blocked, for example, the increase in gastric acid secretion evoked by injections of histamine in the rat, and this effect was shown to be related to the presence of adequate concentrations of the antagonist in plasma. Using radioactive burimamide the time course of plasma concentration of the drug was followed, and was shown to parallel the time course of inhibition of histamine-evoked gastric acid secretion. In addition to this blocking, burimamide also inhibited the secretion of gastric acid evoked by injection of the gastrin analogue pentagastrin.

The polypeptide hormone gastrin is released from the alimentary tract after feeding, and is known to play an important part in triggering gastric acid secretion. Blockade of this response by a histamine H2 antagonist lends powerful support to the hypothesis that gastrin effects are mediated through a local release of histamine in the stomach. On the other hand, gastric acid secretion evoked by stimulation of the vagus nerve to the stomach was not antagonized by burimamide, suggesting that this involves a different mechanism of secretion stimulation. In the cat and dog burimamide had similar effects in blocking gastrin secretion evoked by histamine and pentagastrin. In the dog it was possible to show that burimamide also inhibited the gastric acid secretion evoked by the natural stimulus of feeding, and this suggests that most of the gastric secretion which occurs normally after feeding may be mediated locally by the gastrin/histamine H2 system, rather than by nervous control through the vagus. Preliminary experiments with normal human volunteers also indicate that burimamide is effective in blocking the gastric acid secretory response evoked by pentagastrin.

The studies of Black and his colleagues thus provide valuable new information on the hitherto rather obscure H2 category of histamine receptor. They also provide a valuable new tool, burimamide, for further studies of such systems, and one which may have important clinical

applications. The relative importance of H1 and H2 histamine receptors in the cardiovascular actions of histamine, particularly in local inflammatory responses, is still unclear, but it may now be possible to unravel some of these complexities. Anybody interested in emulating

these elegant studies on other ill defined biological receptors will not have failed to note that the present results were the outcome of eight years of work, involving the synthesis and testing of more than 700 compounds.—From a Correspondent.

Reverse Transcriptase and Transformation

It is hardly an over-exaggeration to say that reverse transcriptase, the enzyme found in 1970 in RNA tumour virus particles which can use the single-stranded RNA genome of those viruses and other RNAs, natural and synthetic, as a template for the synthesis of complementary double-stranded DNA, was discovered because Temin had realized as long ago as the early sixties that the biology of the RNA tumour viruses demands such an enzyme. He maintained, contrary to the canons of molecular biology, that the simplest way to explain the stable and hereditary association between the RNA genome of an RNA tumour virus and the DNA genome of its host cell was to invoke the existence of an enzyme which could copy the genetic information in the viral RNA into a DNA molecule which might then become integrated into the cell genome. And, of course, as soon as an enzyme capable of this reverse transcription was discovered in precisely the place, the virion, Temin had predicted, it was immediately assumed that the enzyme in fact plays the part Temin had assigned to it, namely the synthesis of a DNA provirus.

Unambiguous experimental evidence that infection and transformation of cells by RNA tumour viruses depend absolutely upon the activity of reverse transcriptase has, however, yet to be obtained. Even circumstantial evidence that this is the case has been slow to accumulate, which is why the experiments reported last week in *Nature New Biology* (236, 163; 1972) by Ting, Yang and Gallo merit general attention.

In common with many other groups Gallo and his associates have been investigating the activity of a set of derivatives of rifamycin, the antibiotic which prevents the initiation of transcription by *Escherichia coli* DNA dependent RNA polymerase. These derivatives can be classified into three groups: those which fail to inhibit reverse transcriptase (class A); those which are moderate inhibitors (class B); and those which are very potent inhibitors of the viral enzyme (class C). The significant question to ask is whether the infection and transformation of cells by RNA tumour viruses are blocked by class C derivatives but not by class A derivatives. If the spectrum of inhibition of reverse transcriptase *in vitro* by these drugs is matched by a spectrum of the drug's ability to block establishment of infection by these viruses, there is every reason to conclude that infection depends on reverse transcription.

There is, of course, nothing very new about this argument and experiment, for as long ago as the autumn of 1969 Diggelmann and Weissmann reported in *Nature* (224, 1277; 1969) that the transformation of chick fibroblasts by Rous sarcoma virus can be inhibited with rifampicin. But this experiment, and others like it, is open to the criticism that because the drug was added to the cells soon after their infection it may have inhibited cell multiplication. There is evidence that the efficiency of focus

formation by tumour viruses is affected by the rate at which the cells are multiplying so that it can be argued that the rifampicin blocked the transformation of the fibroblasts not by directly inactivating the RSV reverse transcriptase but by inhibiting cell multiplication.

To avoid this criticism Ting *et al.* preincubated the viruses they were using—mouse sarcoma virus (MSV) and Rauscher murine leukaemia virus (RLV)—in buffered solution of the various rifamycin derivatives, and only after washing the virus particles did they then infect cells or assay *in vitro* for inhibition of reverse transcriptase activity. Furthermore, they assayed enzymatic activity directly by exposing virus particles, which had not been preincubated, to the drugs. Moreover, to facilitate the detection of foci of transformants they used rat NRK cells because foci develop from the clonal growth of initially transformed cells rather than from recruitment by infection of neighbouring cells with progeny virus liberated by the initial transformants.

To cut a long story short, Ting *et al.* found that the class C derivatives, which most potently inhibit reverse transcriptase, block transformation of NRK cells by 95–100 per cent whereas class A derivatives, which have no effect on the enzyme, block transformation by about 25 per cent and class B derivatives inhibit transformation by about 50 per cent. A correlation between inhibition of RNA polymerase activity and loss of infectivity was not observed when similar experiments were repeated with the non-oncogenic but lytic vesicular stomatitis virus, virions of which contain an RNA dependent RNA polymerase. These gratifying results—no doubt precisely what the group must have hoped for—strongly suggest that reverse transcriptase activity is essential for infection of cells by RNA tumour viruses; the only other explanation, which Ting *et al.*, but not everybody, may feel is too trivial to explore, is that viruses preincubated in class C derivatives are less able to adsorb to host cells. This idea ought perhaps to be eliminated by appropriate experiments. Ignoring this possibility, Ting *et al.*'s experiments nicely complement the Hanafusas' investigations of RSV α (0), a strain of Rous sarcoma virus which unaided is unable to infect cells and which also lacks reverse transcriptase.

Pursuing their investigations of these rifamycin derivatives, Gallo and Ting and other associates have investigated the cytotoxicity of the derivatives for fresh human leukocytes from healthy people and leukaemics and for cells of human lymphoblastoid lines of normal and neoplastic origin (*Nature New Biology*, 236, 166; 1972): no doubt at the back of their minds lurks the idea that reverse transcriptases, perhaps of viral origin, play a part in human leukaemia. Having first stimulated the normal leukocytes to divide by exposure to the mitogen PHA, and shown that such stimulated normal cells respond like dividing leukaemic cells to standard clinical

drugs such as methotrexate and daunomycin, Gallo and his colleagues incubated cultures of normal and leukaemic cells with class A, B or C rifamycin derivatives. It turns out that the class C derivatives at concentrations between 20 and 50 $\mu\text{g/ml}$ are markedly more cytotoxic for the leukaemic myeloblasts and lymphoblasts than for the stimulated normal cells. Furthermore, all the derivatives tend if anything to inhibit rather than to enhance what little maturation and differentiation of the leukaemic blast cells occur in soft agar cultures. When cells of established human lymphoblastoid lines were similarly tested no selective cytotoxicity for cells of lines derived from cancer patients was noted. This is not perhaps surprising because lymphoblastoid cells that have been in culture long enough to become established lines have, irrespective of the status of their source, many properties of neoplastic cells.

The molecular basis of the selective cytotoxicity of the class C rifamycins for fresh leukaemic leukocytes is at present far from clear. Most derivatives inhibit DNA polymerases of normal leukocytes to much the same extent as the counterpart enzymes from leukaemic cells, and, as Gallo and his colleagues admit, much more work on cellular polymerases from various sources will have to be done before any clear picture emerges, if indeed inhibition of polymerases is the prime cause of the cytotoxicity of these drugs. Nevertheless, Gallo's group seems quite adamant that, whatever the reason, the class C rifamycin derivatives are selectively cytotoxic for fresh human leukaemic leukocytes.—From our Cell Biology Correspondent.

Model of Fitness

ACCORDING to E. B. Ford, ecological genetics deals with the adjustments and adaptations of wild populations to their environment. Its great success has been to demonstrate the forces of natural selection that are operating in nature; thus, with the aid of models, the changes in the genetical structure of populations can be predicted and the frequencies of the genes explained.

The evolution of industrial melanism is a classic of ecological genetics. When Haldane in 1924 first put forward his simple model of the evolution of melanism, he had to postulate very strong selective forces to explain the rapidity of the evolution. Kettlewell then observed the strong selective forces Haldane had postulated. But in one respect, Haldane's model did not fit the facts. In spite of the selection for the melanics, their frequencies did not reach 100 per cent in industrial areas. Haldane later modified his model to make the heterozygote fitter than the homozygote. This would produce the observed polymorphism with non-melanic forms never completely eliminated by selection. Clarke and Sheppard (*Proc. Roy. Soc., B*, **165**, 424; 1966) obtained estimates of the heterozygotes' advantage from their experiments to measure the selective forces operating in favour of the melanics near Liverpool. The study of the evolution of melanism illustrates the scientific method in action: hypotheses are formulated and then rejected as data are collected to test them; more exact hypotheses are put forward to incorporate the new facts.

But in spite of its many successes in the scientific

explanation of why genes are observed at particular frequencies in natural populations, ecological genetics has hardly ever been concerned with the actual numbers of individuals with different genes. And yet ecology itself is largely the science of population size and its regulation. Until ecological genetics incorporates ecological models of population growth and regulation into its models of relative gene frequencies, it can hardly be fully deserving of its name.

The basic model of population regulation in ecology is given by the equation $d(\log N)/dt = r(1 - N/K)$ which integrates to give the well known logistic law of population growth. It shows that when the population size is small, the population grows exponentially, for the rate of change of $\log N$ is approximately equal to the "intrinsic rate of population increase", r . As the population size approaches K , its rate of increase slows down, finally coming to a stop when $N = K$. This is the size of the population at equilibrium. K is called the "carrying capacity of the population". There is, however, no particular reason for adopting the logistic equation of population growth except that it may fit data on changes of population size. Other equations can easily be suggested which would fit existing data as well as or better than the logistic equation. And if the logistic equation did not fit some data satisfactorily, more terms in higher powers of N could be included in the differential equation, each with appropriate coefficients to be estimated, until eventually a good fit was obtained. The carrying capacity would then be some function of the coefficients which had been introduced. Ecological models of this sort are therefore purely descriptive and not based on any postulated mechanism by which the various coefficients in the equation could be estimated independently of the model. On the other hand, in population genetics, the fitnesses of the different phenotypes and their genetics are open to independent estimation and experiment and particular models can therefore be shown to be false.

Although models in ecology and population genetics may often have a different logical status, it is essential that they should be brought together if ecological genetics is to acquire a theory for the prediction of the numbers, rather than just the relative frequencies, of different genotypes. Bryan Clarke has now achieved this unification of population genetics and ecology with a model of density-dependent selection (*Amer. Nat.*, **106**, 1; 1972).

The chief problem in constructing models of this sort is to derive a suitable function by which the numbers of the different genotypes determine their fitnesses. Clarke in his model allows for both density-independent variations in fitness (fitness in the sense of the classical models of population genetics) and density-dependent variations in fitness. He takes a very simple genetical model of a dominant gene. Thus MM and Mm are genotypes which both produce the phenotype M and the other genotype produces the phenotype m . The density-independent fitnesses of the two phenotypes are w_1 and w_2 . They are absolute fitness, for they represent the actual numbers of offspring produced per individual in the population. Suppose, after the density-independent selection has occurred, the numbers of the phenotypes are N_1 and N_2 . Then Clarke defines the density-dependent fitnesses as $k_1/(k_1 + N_1 + \alpha N_2)$ and $k_2/(k_2 + N_2 + \beta N_1)$. The quantities α and β represent the effect of the numbers of one of the phenotypes on the fitness of the other. If α and β are

both equal to one, the numbers of both phenotypes affect each other equally: if α and β are both zero, the numbers of one phenotype have no effect on the fitness of the other. Clarke's definition means that the density-dependent fitnesses must lie in the range from one when numbers are low to zero when numbers tend to infinity.

Not only is Clarke's model genetically reasonable with fitnesses lying in the correct range of values, but it also produces a logistic model of population growth, and is therefore ecologically reasonable too. Thus, if the population is monomorphic with only one phenotype, say m , present, Clarke's model is then approximately the same as the logistic equation.

Clarke shows by his analysis of the model that there is a wide range of values of the parameters which allow for the establishment of balanced polymorphisms. It is interesting that when the numbers are low, the density-independent selective values determine the spread or elimination of the gene and selection is mainly for increased reproductive rate. Selection of this sort has been called " r " selection as opposed to " K " selection for increasing the carrying capacity of the population. Both types of selection are incorporated in Clarke's model. Darwin himself was well aware that selection for increased reproductive rates, or r selection, would not by itself increase the final size of the population and Clarke's model makes these ideas quantitative. Clarke also shows that in his model a polymorphic population consisting of both phenotypes will generally be larger than a monomorphic one. Thus his model describes quantitatively another fact which Darwin had originally noticed.

In the *Origin of Species*, Darwin explained that populations of mixtures of different varieties produce greater yields than populations of only one variety: if different varieties have slightly different environmental requirements they will compete less as individuals than the individuals of a single variety all competing for the same requirements. Clarke gives the conditions that a polymorphic population should be larger than a monomorphic one. They can be stated in terms of the carrying capacities, K_1 and K_2 , of the two monomorphic populations. In Clarke's notation K_1 and K_2 are equal to $k_1(w_1 - 1)$ and $k_2(w_2 - 1)$ and his conditions are then $\alpha < K_1/K_2$ and $\beta < K_2/K_1$. For example, if both phenotypes have the same monomorphic carrying capacities, and will both therefore reach the same final population size, then the inequalities show that α and β must both be less than one if the polymorphic population is to be larger than the monomorphic ones. This simply means that the fitness of one phenotype must be reduced less

by a given number of individuals of the other phenotype than by the same number of its own phenotype. The model gives an exact quantitative expression to Darwin's idea.

Thus, for the first time, there is now an ecological and genetical model which combines the essential observed features of both ecological and genetical data. Bryan Clarke has produced a simple and realistic model which is the first step towards a theoretical ecological genetics. —From our Population Genetics Correspondent.

TUMOUR VIRUSES

Unexpected Integration

from our Cell Biology Correspondent

WHEN polyoma virus or simian virus 40 infects and transforms a non-permissive cell, viral genomes are apparently stably integrated in the host genome such that they are transcribed and also inherited as the transformed cells multiply. When, by contrast, these viruses replicate in the nuclei of permissive cells, which eventually lyse, it has generally been assumed that the replicating viral genomes remain free and independent of the host genome. The argument has always been why com-

plicate the issue by invoking integration during the lytic cycle in the absence of any data which might hint of integration in such circumstances?

Of recent months, however, the notion that SV40 or polyoma virus genomes might integrate into permissive host cell genomes has become noticeably more widely mentioned as a possibility yet to be excluded. Now the latest issue of the *Journal of Virology* contains a pair of reports, by Lavi and Winocour and by Tai, Smith, Sharp and Vinograd (9, 309 and 317; 1972), which indicate that during the replication of SV40 in permissive cells recombination events leading to the integration and excision of the viral DNA can and do occur even though they may not be a prerequisite of the replication of the virus.

Winocour and his colleagues reported in 1969 that DNA extracted from SV40 particles which had been grown on BSC 1 cells hybridized to a significant extent with BSC 1 DNA, from which they concluded that host DNA had become covalently incorporated into at least some of the viral DNA molecules. When other groups failed to repeat these observations, however, there was a widespread tendency to disregard them. But Winocour per-

TD-1A Looks at Stellar Atmospheres

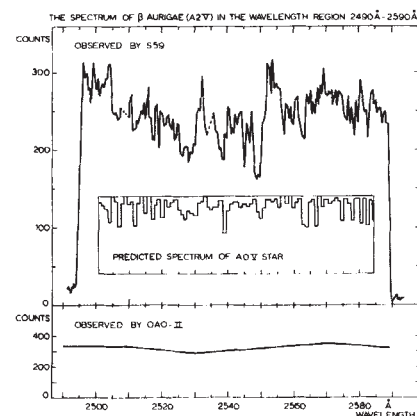
NEXT Monday's *Nature Physical Science* (April 24) contains data from the first satellite equipped to obtain high resolution spectra of stars in the ultraviolet between 2000 Å and 3000 Å. The illustration shows part of the spectrum of the first star to be observed, β Aurigae, with for comparison a spectrum of the same object obtained by the Orbiting Astronomical Observatory OAO 2 which had lower resolution.

The spectrum was obtained by the European satellite TD-1A on March 20, a week after its launch from the Western Test Range, and is reproduced in an account of the functioning of the ultraviolet spectrometer by the Dutch group responsible. They also show a spectrum of β Aurigae near 2800 Å, in which the Mg II lines which are expected to give new information on the physical conditions in the outer stellar atmosphere are prominent.

The Dutch group explain that the experiment was proposed by Professor C. de Jager (Astronomical Institute, Utrecht), and that spectra can be obtained in three wavelength bands of width 90 Å, centred near 2110 Å, 2540 Å and 2820 Å. The spectral resolution is 1.8 Å. Detailed ultraviolet spectra will be valuable for the information they are expected to give about

conditions in the atmospheres of young stars which also tend to be hot.

In the first sequence of observations spectra were obtained for γ Columbae (magnitude 4.35) and 67 Ophiuchi (magnitude 3.97) as well as for β Aurigae (magnitude 1.90). According to the Dutch group it will be possible to observe two hundred stars of spectral types O, B and A brighter than magnitude 4.5.



Spectrum of β Aurigae, the first star to be observed with the stellar spectrophotometer on board the European satellite TD-1A, with for comparison the predicted spectrum for a star of type AO and a spectrum obtained by the Wisconsin package on OAO 2.

severed, and now with Lavi has come up with confirmation of his group's original data and an explanation of subsequent discrepancies; everything apparently depends on the multiplicity of infection of the cells from which virus is collected.

When BSC 1 cells are infected at a low multiplicity (0.032 p.f.u./cell) with non-plaque purified virus, little if any of the SV40 DNA that can be recovered from the infected cells hybridizes to BSC 1 DNA. But as the multiplicity of infection is increased a correspondingly increasing amount of viral DNA, isolated from the infected cells or the progeny virions they liberate, hybridizes with cell DNA. Similarly, as plaque purified virus, which does not hybridize with host DNA, is serially passaged, so the viral DNA gains sequences complementary to host DNA.

From these data Lavi and Winocour suggest that "native" plaque purified SV40 viral DNA can probably recombine only at a few sites in the host genome, but when integrated genomes are excised they may pick up segments of host DNA and lose part of the viral genome. At high multiplicities such DNAs will replicate because complementation may provide the missing viral functions, and because they carry host DNA they may more frequently integrate and excise. As the process repeats itself on serial passage, an increasing proportion of the virions will contain DNA molecules carrying segments of host DNA.

The experiments of Tai *et al.* largely support these arguments. By denaturing and then allowing to renature the DNA of SV40 virus particles obtained from BSC 1 cells infected at high or low multiplicities, they have produced heteroduplex molecules of SV40 DNA. Under the electron microscope heteroduplex molecules with inhomogeneities—variously positioned loops of single stranded DNA in otherwise double stranded molecules—can be seen. These arise from deletions and/or substitutions of DNA. The number and pattern of such inhomogeneous molecules correlate with the history of the virus stocks. DNA from virus passaged at low multiplicities gave rise to inhomogeneous heteroduplexes which indicate that 2 per cent of the starting DNA was deleted and substitutions were undetectable.

Analysis of heteroduplexes of DNA of viruses passaged at high multiplicities, by contrast, revealed that 7–12 per cent of the original molecules had substitutions and 11–13 per cent had deletions. In the substituted molecules some 30 per cent (range 10–60 per cent) of the native SV40 DNA seemed to have been replaced by DNA, on average only 20 per cent (range 5–50 per cent) of the length of the intact

SV40 DNA molecule. In short, serial passage at high multiplicities leads to deletions and deletion-substitutions, and taking account of Lavi and Winocour's data the substituted DNA is probably cellular and not viral.

The implications of these findings are obviously far reaching not least because, as Tai *et al.* say, "there may be fewer differences between the lytic and transformational events induced by SV40 than once thought".

ANIMAL LOCOMOTION

Hovering Flight

from our Insect Physiology Correspondent
LARGE birds and large insects make extensive use of gliding flight; even when the wings are beating, the forward movement of the body contributes extensively to the lift. But in both groups small species have evolved from larger ancestors, and it is these small forms which have been able to exploit the aerial medium to the full and to occupy the small niches in the aerial biosphere by hovering in stationary flight and flying backwards or very slowly forwards.

Hovering flight is familiar enough as an everyday phenomenon; but only in a recent article by Torkel Weis-Fogh (*J. Exp. Biol.*, **56**, 79; 1972) have the aerodynamics and the energy balance of the process been fully analysed for the first time. Weis-Fogh has chosen the fruit fly *Drosophila* and the humming-birds as representative types, both of which hover and fly forwards or backwards with fully extended wings during the entire wing-stroke cycle. Sufficient observational data on both have been published in recent years to make possible realistic calculations of the forces involved in the hovering flight of these two groups.

Of all types of locomotion in animals, hovering flight makes the heaviest demands for power. It is more costly than ordinary flapping flight because the body has no accumulated kinetic energy that can contribute to lift, as in forward flight; support depends solely on the continued movement of the wings. So far as aerodynamics is concerned, Weis-Fogh shows that in both *Drosophila*, with a Reynolds number of 100, and the humming-bird, with a Reynolds number of 10,000, hovering flight is chiefly consistent with steady-state aerodynamics,

Thermal Cycling Effects in Polymers and Metals

CREEP in polymers has certain resemblances to creep in metals from the phenomenological standpoint in that both may be attributed to the thermally activated movement of defects. In metals these defects may be interstitial atoms, grain boundaries or dislocations, whereas in a polymer they can be considered to be small segments of polymer chains which can rotate or change their positions. In both cases a first approximation to the creep behaviour is to consider a single relaxation time model which obeys the laws of linear viscoelasticity. The time-temperature superposition principle then leads to an equation for the activation energy ΔH of the process. This may be experimentally determined in creep by measurements at a series of different temperatures and the use of the superposition principle to find the shift factor a_T from which ΔH may be found.

If the creep behaviour is non-linear, however, this method fails and more complicated expressions involving multiple integrals have been proposed as in the Green-Rivlin theory. In this context the significance of activation energy is not easy to see.

Another method used in the study of the creep of metals is to change the temperature rapidly from T_0 to T at some time t' during a creep experiment and to determine the rates of change of creep strain before and after the

change in temperature. The ratio of these then gives the shift factor a_T from which ΔH can be found as before. This method could then be extended into the non-linear region. For metals the method works well and its limitations have been considered by McCrum and Morris (*Phil. Mag.*, **7**, 2115; 1962).

In next Monday's *Nature Physical Science* (April 24), Hutchinson and McCrum describe a test of the method for determining the activation energy of creep in high density polyethylene at low strain, where the result should coincide with the known value of 30 kcalorie mol⁻¹. Surprisingly an anomaly, or rather two anomalies, occur in that for positive temperature increments higher activation energies are found and for negative increments lower values, neither being anywhere near the true value. These anomalies are resolved by assuming that any thermal fluctuation during a creep experiment always increases the creep rate in a manner analogous to the behaviour of α -uranium and held to be attributable to the effects of differential thermal expansion of the anisotropic crystals of which both polymer and metal are composed.

It these effects are found to occur in most crystalline polymers further support will be added to the view that the more significant advances in understanding of polymers now come from physics rather than from chemistry.

though in the case of *Drosophila* drag effects dominate—it resembles an aircraft working at the limit of its ability with almost nothing to spare for manoeuvres.

The trouble about an oscillating propeller, as provided by wings beating at a frequency of 35 per second in the humming-bird or 250 per second in the fruit fly, is the enormous amount of energy involved in the stopping and starting of the wings twice in each cycle. In insects, as was shown a good many years ago by Weis-Fogh, not more than 15 per cent of this energy is degenerated into heat; at least 85 per cent is stored as elastic energy and released as kinetic energy during the reversed stroke. This elastic storage is effected by the solid skeletal cuticle of the thoracic wall, by the remarkable elastomer resilin in the wing hinges and wing stops, and by an elastic component in the myofibrils themselves.

It seems that the humming-bird is unable to make economies of this kind: elastic components in the opposing muscles are poorly developed; the osseous internal skeleton lacks suitable elasticity; and although elastin—the common elastomer in vertebrates—can serve this purpose during running and walking, its damping properties rise so steeply at high frequencies of oscillation that it cannot operate effectively in the beating wings. It looks as though the vertebrates selected the wrong elastomer at an early stage of evolution—before flight was envisaged.

SOLAR SYSTEM

Too Many Cooks

from a Correspondent

THE origin of the solar system is one of the oldest unsolved problems in natural philosophy, and at a discussion meeting organized jointly by the Royal Society and the Royal Astronomical Society on March 27 astronomers and space scientists once again learnt that there are as many theories on the subject as there are researchers in the field. Dr D. Ter Haar (University of Oxford) went so far as to suggest that a solution is no nearer now than it was in René Descartes's time 340 years ago.

Theories proliferate because of the scarcity of facts. At present the chief facts which have to be explained are: (1) the regularity of the system—the planets move in prograde, near circular orbits and have isochronous spins about axes which are largely perpendicular to the ecliptic; (2) the satellite distribution around a planet is similar to the planetary distribution around the Sun; (3) the division into an inner group of small, dense, satellite-free planets and an outer group of large, low density, multisatellite planets; (4) the peculiar regularities

in the planetary and satellite spacings, summed up by the Titius-Bode law; and finally (5) the distribution of angular momentum and mass between the Sun and the planets.

Most of the theories which have been propounded had the planets condensing out of a nebula of gas and dust surrounding the Sun. Where the nebula came from and why, and whether or not it postdated the Sun, were questions left unanswered. Dr Ter Haar showed that turbulent eddies could lead to condensations with different compositions and densities, and these differences are caused by the decrease in nebula temperature as the planet moves away from the Sun. A serious problem arises here because the accretion of a planet would take about 10^8 yr and this is a factor 10^5 greater than the eddy lifetime. Dr Ter Haar also stressed the important similarities between planet and satellite formation.

Discussing the angular momentum deficiency of the Sun, Professor G. Arrhenius (Scripps Institution of Oceanography) concluded that magneto-hydrodynamic breaking must have occurred and that this ionized the nebula. He discussed recent experiments on the condensation of magnesium silicate and glasses from cold (a few hundred degrees Kelvin) rarefied

plasmas, and concluded that meteorites have been formed by direct condensation and not by secondary processes in planetary mantles.

Professor N. M. Woolfson (University of York) drew the audience back to the stellar approach theory of Jeans, but with a difference, because he suggested that the planet-forming material was drawn out of the passing star and not from the Sun. Dr D. G. King-Hele (Royal Aircraft Establishment, Farnborough) then delved into the realms of mysticism and numerology as he amusingly told of the empathic mythopia of the poetical descriptions of the birth of the solar system and also the numerical juggling which produced the Pythagorean harmony of the spheres and the Keplerian solution which used a nest of regular polyhedra. By extending the Titius-Bode law he showed that there are very significant relationships between the parameters of the different planetary orbits. Professor W. H. McCrea (University of Sussex) discussed the protoplanet theory in which, for example, Earth, Mars and the Moon were all formed from one large body which became unstable and broke up.

Professor S. K. Runcorn (University of Newcastle upon Tyne) summed up by reminding the audience that a sure way forward was to look for more

Lysogeny at Random in *Escherichia coli*

AT the root of the lysogeny of *Escherichia coli* cells by the bacteriophage λ lies a recombination event between a part of the circular phage chromosome and a specific site in the host cell chromosome. In other words, unique phage and cell DNA sequences recognize each other and the λ DNA is integrated at the recognition or attachment site. P2, another lysogenic phage, is somewhat more catholic than phage λ , for it can integrate at more than one site, but still a limited number of sites, in the host chromosome. Phage Mu-1 is remarkable, however, for its extreme catholicity; it seems to be able to integrate at virtually any site in the *E. coli* K12 genome. Does this mean that a base sequence specifically recognized by the Mu-1 DNA is repeated at countless sites in the bacterial chromosome, or does the Mu-1 integration machinery integrate the Mu-1 DNA at any site regardless of the host base sequence? Experiments reported by Bukhari and Zipser in next Wednesday's *Nature New Biology* (April 26) clearly indicate that the latter alternative is indeed the case; the base sequence of the host DNA seems to be irrelevant to integration of Mu-1 DNA.

Bukhari and Zipser have established this by analysing the pattern of integration of Mu-1 DNA within the *z* gene

of the lactose operon, with which they are very familiar. In essence, by deletion mapping, they have shown that the phage DNA can integrate at at least seventy-six sites in this one gene, which is tantamount to proving that integration can occur at random in this gene and presumably therefore in other *E. coli* genes.

Irrespective therefore of whether or not one special region of the Mu-1 DNA is involved in integration, a point which Bukhari and Zipser are pursuing, it is obvious that specific host sequences are not required, a finding which should greatly stimulate efforts to isolate and characterize the Mu-1 integration enzymes.

Bukhari and Zipser have also observed that recombination between two strains carrying Mu-1 DNA integrated at close but not identical sites in the *z* gene is a very rare event. It also seems that the presence of the Mu-1 DNA somehow excludes recombination in adjacent regions of the *z* gene, and this is not the result of deletion of host DNA caused by integration of the phage DNA. It seems more likely, according to Bukhari and Zipser, that the pairing of the prophages themselves on mating throws out of alignment adjacent host DNAs and therefore prevents crossovers of host DNA.

factual stepping stones. The Earth has had its surfaces continuously reshaped by erosion, but on the Moon, for example, a primaevial surface still shows the scars formed in the final stages of mass accretion. Farther afield it might soon be possible to study the planetary systems recently discovered around some of the nearest stars.

CANCER RESEARCH

Initiation of Tumours

from a Correspondent

AT the eleventh meeting in the principles of experimental and clinical oncology series in the British Museum (Natural History) on March 20, the speakers were Dr M. Balls (University of East Anglia) and Dr A. M. Neville (Institute of Cancer Research).

Dr Balls, speaking first, set out to be provocative. As a developmental biologist there were many facets of the thoughts of those interested in cancer with which he was unsympathetic. For his part he did not believe that cancer should be thought of as a disease of cells nor of homotypic collections of cells, but a disease of (developmentally) heterotypic cells. His thesis was that it is the changed relationship between heterotypic cells which is most important in the initiation of tumours.

Speaking of differentiation in general, Dr Balls said that nuclear transplantation experiments had established that differentiation did not involve irreversible genomic changes—by inference he did not feel that such changes were a necessary prerequisite of adoption of the malignant state. Furthermore, passage of macromolecules between cells was accepted as an important component of differentiations mechanisms. No cell—including a malignant cell—in a metazoan organism should be thought of as an island.

Describing the various classes of cells which could be recognized by the developmental biologist, such as pre-competent (not inducible) and competent (responsive to extracellular forces by becoming determined) cells, Dr Balls went on to say that expression of a determined characteristic could be delayed for very many cell generations after the determining event. He therefore found no special mystery in the phenomenon of latency in relation to tumour development. He indicated that interaction between mesenchymal and epidermal cells could lead to maintenance of a differentiated function in the epidermal cells or even modulation of their behaviour. He exemplified this by the rather atypical reaction which is demonstrable between skin or gizzard mesenchyme and skin epidermis. This last tissue when separated from

mesenchyme, tends to undergo end-cell keratinization. When placed in contact with skin mesenchyme it will tend to maintain keratin production and the capacity for replacement of cells, and when placed in contact with gizzard mesenchyme it can produce cilia and mucin. This last modulation is reversible. On the basis of observations such as these Dr Balls felt that it was at least possible to propose that the changes which lead to the production of a malignant cell population probably include changes which are external to the potentially malignant cells.

Dr Neville gave a critical account of tumour index substances, some of which seem to be materials normally produced only, or only in large quantities, during foetal life. He identified as substances of interest in relation to diagnosis or prognosis of tumours, hormones, isozymes, phase specific proteins, α -foetoprotein, carcino-embryonic antigen, foetal sulpho-glycoproteins and α 2-H-foetoproteins. All of these substances had their intrinsic interest; none of them seemed on the basis of the present evidence to be unequivocal indicators of malignancy for diagnostic purposes, but many could be used as indices of progress during cancer therapy.

DIPHTHERIA

What Makes Toxin Tick?

from our Molecular Biology Correspondent

THE work, chiefly of Pappenheimer and his colleagues, in laying bare the mechanism of action of diphtheria toxin is as

pretty a piece of what might be called molecular aetiology as would bring tears of pleasure to the eyes of the departed pioneers of bacteriology. The toxin is a protein of molecular weight 60–65,000, which is progressively cleaved by proteases in the cell extract into pieces of 24,000 (A) and 38,000 (B) that remain bound together by a disulphide bond. The same effect can be achieved, as was shown last year by Gill and Dinis, and by Collier and Kandel, by treatment with trypsin. After reduction, the pieces may be separated, and it is found that the biochemical activity resides in the smaller of the two. This activity is the specific inhibition of eukaryotic translocase, which brings protein synthesis to an instant halt. It achieves this effect by an NAD-dependent ribosylation. The fragment possesses no toxicity in animals, however, which prompts the attractive hypothesis that the other part of the toxin is needed to carry the molecule through the cell membrane and into the cytoplasm, where it can do its work.

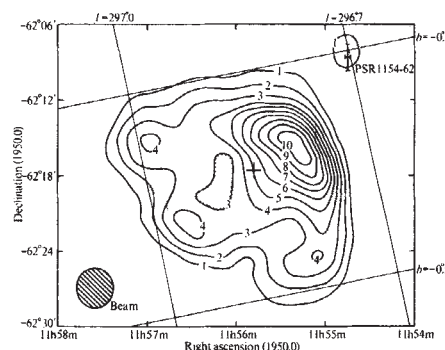
Last year Uchida, Gill and Pappenheimer reported the isolation of a mutant form of the toxin from lysogenized bacteria, which possesses no toxicity, and has a molecular weight of 45,000. Nevertheless it is enzymatically active, and on proteolysis and reduction yields a functional A-fragment. Uchida, Pappenheimer and Harper (*Science*, 175, 901; 1972) have now prepared a new mutant of the lysogenic phage, with a missense mutation in the toxin gene, that generates a strain of the diphtheria bacterium with an inactive toxin molecule, which has normal molecular

Association of Pulsars with Supernova Remnants

THE high velocities of pulsars seem to be consistent with the view that they were ejected from supernova explosions. This makes it difficult to determine with certainty definite pulsar-supernova remnant associations, and even in the Crab there remains some doubt about whether or not there is a "runaway" pulsar associated with the system, as well as NP 5032. But M. I. Large and A. E. Vaughan have now established that there is a good likelihood that PSR 1154-62 is associated with the galactic radio source G296.8-0.3, the Crux supernova remnant (*Nature Physical Science*, next Monday, April 24).

Observations of the radio source made with the Molonglo Cross (see figure) show the shell structure of the source and its proximity to the pulsar. Although PSR 1154-62 lies outside the shell border, it has a velocity of more than 300 km s⁻¹, sufficient to account for its present position, if it was indeed formed with such a velocity, in the Crux supernova.

Furthermore, the age of the remnant (2.5×10^4 yr) is not inconsistent with the presumed age of the pulsar (10^4 to 10^6 yr) and it is interesting that, as in the case of the Vela remnant and PSR 0833-45, the pulsar is adjacent to the brightest region of the shell source. On balance, it seems likely that the juxtaposition of the Crux remnant and PSR 1154-62 on the sky is not a chance occurrence.



weight and an immunological response indistinguishable from that of the functional species. Proteolysis and reduction lead, as usual, to A and B fragments, indistinguishable in detergent gel electrophoresis from those of the wild type cells, but neither in the A-fragment nor in the nicked unreduced molecule is there any detectable blocking activity towards translocase. Labelled NAD does not bind to the mutant fragment, nor will the latter inhibit complex formation between normal A-fragment, NAD and the translocase. It thus seems likely that the mutation is in the NAD-binding site.

The other end of the toxin molecule—the B-fragment—on the other hand, seems to be fully operative, for it will compete with active toxin on equal terms for the attachment sites on HeLa cells, as shown by the way in which it will prevent it from inhibiting the incorporation of labelled amino-acids into protein. By contrast, the low molecular weight mutant, missing the greater part of the B-chain, is incapable of any such competition.

The clinching experiment now follows: mixtures of the two mutant proteins, one defective in the A, the other in the B part, both almost wholly in the form of intact, un-nicked chains, generated a low level of activity on standing, and this was elevated to appreciable levels by the presence of a thiol reagent. Uchida *et al.* inferred that fragment hybridization by disulphide exchange was going on within the nicked fraction of the protein, and indeed when the protein was treated with trypsin and then the thiol, the level of toxicity which was generated increased greatly. In the absence of thiol, electrophoresis shows only two important components, corresponding to the total chains of 62,000 and 45,000 molecular weight, enzymatic activity being associated with the latter. After exposure to the thiol, and reoxidation, enzymatic activity appeared in the higher molecular weight zone to an extent corresponding to about half the concentration of this species. The toxicity in animals after this treatment was 40–80 per cent of the calculated maximal value, and could be specifically inhibited by antitoxin. It is thus established that the part of the chain corresponding to the B-fragment is indeed implicated in penetration of the cell membrane, and opens the door, so to speak, for entry of the instrument of destruction, the A-fragment.

From the nature of the B-mutation, Uchida *et al.* had deduced that this fragment occupies the C-terminal part of the intact toxin chain. Michel *et al.* (*Biochim. Biophys. Acta*, 257, 249; 1972) have now confirmed this directly. They have separated the fragments from the nicked toxin, and determined the

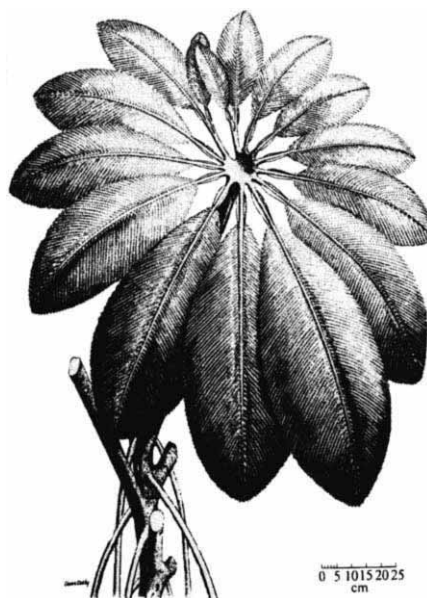
end groups of both. Assuming, as it is reasonable to do, that the naturally generated fragments can be identified with the products of trypsin treatment, it turns out that the A-chain has a glycine N-terminus, as for the most part has the intact toxin, whereas from the B-chain four N-terminal species can be isolated, among which serine and glycine predominate. At the C-terminal end, the toxin has arginine, and the A-chain arginine and histidine in a ratio of 2:1, whereas the B-chain has a variety of amino-acids. The sequence of the first fifteen N-terminal residues of the A-chain is also reported.

The endogenous protease thus evidently produces untidy ends, and the A-chain in fact shows electrophoretic microheterogeneity. The formation of new C-termini in the A-chain and N-termini in the B-chain establishes the C-terminal position of the latter in the toxin. The prevalence of C-terminal arginines suggests a trypsin-like specificity of the protease. It must be supposed that A and B are globular entities joined by an exposed segment of chain, which is vulnerable to proteolysis. Some amino-acids must be presumed lost in the digestion process, but the additivity of the molecular weights of the A and B pieces indicates that these cannot comprise more than a few residues. There must be at least two arginines in this connecting segment, one flanked by a glycine on the carboxyl side, the other by a serine. The presence of small amounts of three N-terminal

amino-acids besides glycine in the intact toxin is unexplained.

PALAEOBOTANY

Wealden Fern



This is a reconstruction of the Cretaceous fern *Weichselia reticulata* which has been prepared by Mrs C. Dalby for K. L. Alvin's new monograph on specimens of the species collected from the Wealden of Belgium (*Mem. Inst. Roy. Sci. Nat. Belg.*, No. 166; 1971). The figure, about 1/25 natural size, shows the stem with petioles, the rooting organs (unique among ferns), the aerophores and one complete vegetative frond.

Cyclic AMP and Cell Adhesion

TRANSFORMED cells growing in tissue culture exhibit a wide range of phenotypic traits not shown by cultures of comparable but untransformed cells. Transformants, for example, have a changed morphology and a changed cell surface; they usually continue to multiply in serum concentrations too low to support the multiplication of untransformed cells; they adhere less tenaciously to their substratum than untransformed cells and sometimes grow in suspension culture; and, most importantly, they grow to very much higher saturation densities than their untransformed counterparts. In other words transformed cells are less susceptible to contact inhibition of growth.

Over the past several months it has been shown that when appropriate concentrations of cyclic AMP and of theophylline, which inhibits cyclic AMPase, are added to cultures of transformed cells many of these phenotypic traits are reversed and the transformants begin to behave as if they had not been transformed. In *Nature New Biology*

next week (April 26) Johnson and Pastan add the tenacity of adhesion of fibroblasts to their substratum to the growing tally of characters which can be changed by manipulating the concentration of cyclic AMP and theophylline.

Johnson and Pastan have taken cultures of mouse fibroblasts, L-929 cells and SV40 transformed 3T3 cells and measured the time required to detach 50 per cent of the cells in a culture with 0.02 per cent trypsin in the presence or absence of cyclic AMP and theophylline. Without the additives half the L-929 cells and SV3T3 cells growing in Johnson and Pastan's conditions are detached in 16 min and 12 min respectively, while after 30 min or 3 days' incubation in the presence of cyclic AMP and theophylline these times are increased to 47 min and 22 min respectively. Furthermore, this increased adhesiveness of mouse fibroblasts growing in the presence of cyclic AMP is not inhibited by cycloheximide but it is antagonized by serum and is fully reversible.

Black Holes and Gravitational Theory

ROGER PENROSE

Department of Mathematics, Birkbeck College, London

There have been several recent claims to have detected black holes. In this article Professor Penrose describes the theoretical basis of black holes and some of the recent thinking on the subject.

AFTER about 10^{10} yr, according to accepted theory, our Sun will first expand and become a red giant (swallowing the Earth in the process) and then contract to a white dwarf—a star of mere planetary dimensions. Further contraction will be prevented by electron degeneracy pressure (a consequence of the exclusion principle as applied to electrons). As Chandrasekhar¹ showed in 1931, however, a non-rotating star of mass greater than about $1.3 M_{\odot}$ (where $M_{\odot}$ is the mass of the Sun) cannot ultimately sustain itself in this way against further gravitational collapse. Stars of up to about $50 M_{\odot}$ are known to exist, so the question of their eventual fate is a very real one. Although this question was largely answered by Oppenheimer and Snyder² in 1939, most astronomers paid little attention, apparently believing that in the final stage of collapse sufficient material would always be ejected to bring the mass of the resulting body down to below the Chandrasekhar limit—or to below the Oppenheimer–Volkoff³ limit which is the corresponding maximum mass (variously denominated in the range $0.7 M_{\odot}$ – $3 M_{\odot}$) of a neutron star (far denser even than a white dwarf, the density being comparable with that inside an atomic nucleus) in which it is neutron degeneracy pressure which sustains the star against gravitational collapse. (Neutron stars are observed in pulsars, and for a mass of about $1 M_{\odot}$, the radius of a neutron star should be roughly 10 km.) The Oppenheimer–Snyder picture was not, until recently, generally accepted because of its very strangeness. It is this picture which has come to be referred to as that of a black hole and which I shall be concerned with here.

No Escape

The characteristic feature of a black hole is that it represents a region of space into which the body has fallen, but from which no form of matter, energy, or information can escape. (A $1 M_{\odot}$ black hole has a radius of about 3 km—only a little less than that of a neutron star.) The body itself will have fallen deep inside the black hole and possibly been crushed out of existence. Nevertheless, the black hole itself still exerts a gravitational pull on other bodies, so it is not totally unobservable. But the detection of black holes is difficult. It is only within the past year or so that claims have been seriously put forward that the invisible companions of certain stars belonging to binary systems (or of larger systems such as globular clusters) may indeed be black holes^{4–15}. The detection of a black hole may be through its gravitational effect on the companion star, through its gravitational effect on material in the neighbourhood of one or both “stars”, or through the possible emission of X-rays (or even of gravitational waves), as the surrounding material is inexorably, but very slowly, funnelled into the black hole. Alternative (“conventional”) explanations seem still to be available for all these black hole candidates so far put forward, but this situation may not persist for long.

It should be pointed out, however, that the evidence which might seem most conclusive for the existence of a black hole, namely that there be a completely dark object of mass too great to be either a white dwarf or neutron star, is of rather negative character. Theory predicts that such dark “objects” (that is, black holes) should exist, but observations of this kind could hardly be regarded as very strong evidence for the theory. One could conceive that theory might really be very wrong, insofar as it forbids the existence of objects of the nature of white dwarfs or neutron stars that are too massive. If, however, an intensive search over several years fails to confirm the existence of dark “objects” of mass greater than $3 M_{\odot}$, then this would be exceedingly uncomfortable for present theory.

I shall consider the black-hole concept and explore the theoretical reasons for believing that black holes should exist. Although most of the discussion of black holes is carried on within the framework of Einstein’s general theory of relativity, the existence of a phenomenon of this type is not so very critically dependent on the particular theory of gravity which is used. Indeed, even within the framework of Newtonian theory it was predicted, as long ago as 1798 by Laplace¹⁶, that (as quoted by Eddington¹⁷) “the largest luminous bodies in the universe may, through this cause, be invisible to us”. Laplace’s argument was that for sufficiently massive and condensed bodies the escape velocity at the surface would exceed the velocity of light. Thus all emitted light would be dragged back, rendering the object invisible. In particular, Laplace points out that “A luminous star, of the same density as the Earth, and whose diameter should be 250 times that of the Sun, would not, in consequence of its attraction, allow any of its rays to arrive at us”. It is worth noting that the formula expressing the condition for this to take place is $2mGc^{-2} > r$, in Newton’s theory, where m and r are the mass and radius of the body, G the gravitational constant and c the speed of light. This is the same formula as that given by Einstein’s theory, expressing the condition that the body should be trapped inside a black hole.

Not all theories of gravitation, however, predict the existence of such a phenomenon. In particular, the scalar gravitational theory of Nördstrom does not lead to a picture of this kind. This is because in Nördstrom’s theory, light is not deflected in a gravitational field. In general, the black-hole phenomenon is a consequence of the fact that light is attracted by gravitating bodies—an observed effect (which, incidentally, can be regarded as observational disproof of Nördstrom’s theory). The general principle involved—that in a powerful enough (spherically symmetrical) gravitational field, light cannot escape and inevitably falls in towards the centre of attraction—is largely independent of the details of the theory of gravitation used, provided that light is sufficiently attracted by gravity in a way similar to matter. The point is roughly that once the escape velocity exceeds that of light, then (assuming that special relativity holds locally so that the light velocity is the limiting velocity) nothing can escape. Indeed, in the theory of gravity which at the present time may be regarded as the most serious rival to general relativity, namely the (Jordan)–Brans–Dicke theory¹⁸, black holes (essentially identical to those predicted by general relativity) develop^{19,20}.

I shall, for the moment, confine attention to general relativity and describe first the standard (Oppenheimer–Snyder) picture of spherically symmetrical gravitational collapse to a

black hole. Then I shall consider the effect that deviations from spherical symmetry may be expected to have in the light of some recent theoretical results in general relativistic black-hole physics. Finally, I shall discuss some more conjectural aspects, in particular in relation to Weber's remarkable observations²¹, apparently of gravitational waves emanating from the centre of our Galaxy.

To obtain the picture of spherically symmetrical gravitational collapse, we envisage matter falling radially inwards towards some central point and suppose that the pressures are not large enough to counter the gravitational pull. (Indeed, in general relativity, pressure itself is a source of extra gravitational attraction. When the matter is sufficiently concentrated, the additional gravitational pull due to pressure more than overcomes the direct effect of the pressure itself. Greater pressure then increases the tendency to collapse.)

After the matter has fallen to within a radius $r=r_m=2mGc^{-2}$ (the Schwarzschild radius) curious things happen, for light emitted from the surface of the matter falls inwards (Fig. 1). (At $r=r_m$, emitted light can "mark time", hovering for ever at the same distance from the centre.)

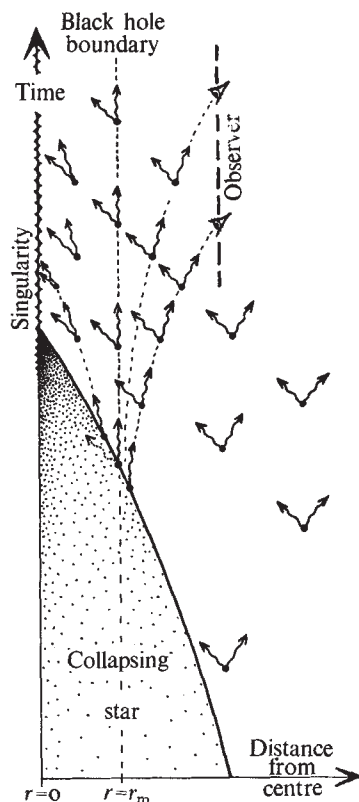


Fig. 1 The history of a spherically symmetrical star collapsing to form a black hole. The wavy arrows at each point indicate how an ingoing or outgoing light flash propagates.

It is clear from Fig. 1 that an observer outside the hole cannot see the matter after it has fallen in. In principle, however, he can always still see the matter just before it fell through the hole. This is because as the surface of the body approaches $r=r_m$, the light it emits takes longer and longer to escape, the escape time being theoretically infinite from $r=r_m$. But in practice the observer would receive essentially no light from the matter after a short time. This is because only a limited amount of light is emitted before the body reaches $r=r_m$, whereas this limited amount has to be received over an infinite time-span by the observer. Thus the observer sees the light increasingly redshifted, the intensity dying off

very rapidly—exponentially, in fact, with a time-scale of the order of milliseconds for the case of a body of a solar mass or so. A black hole is then all that the observer perceives²².

But what happens to the matter itself after it has fallen through the hole? According to the spherically symmetric general-relativistic picture, the matter inevitably gets crushed to greater and greater densities—without any limit. Within a finite time (milliseconds again, for a solar mass) the density becomes infinite, the curvature of space-time also becoming infinite so that a singularity in the space-time at the centre is the result².

How does such a space-time singularity manifest itself in physical terms? This can be answered by imagining an observer falling inwards through the hole, following the matter towards the centre. The effect of space-time curvature on the observer is that he experiences tidal forces. He feels himself to be stretched in one direction (namely in a line extending through himself to the central point) and to be squashed in the perpendicular directions. As he falls towards the centre this tidal effect increases and, indeed, for a solar mass this tidal effect would be easily enough to kill a man even before he reached the hole. But for larger masses (for example the 10^6 to $10^8 M_\odot$ range that some astrophysicists believe would be appropriate for a black hole situated at the centre of the Galaxy), these tidal forces would be quite small until the observer is well within the hole. But as he nears the centre, the effect mounts inexorably. Not only is the observer himself soon destroyed by the mounting space-time curvature, but the very atoms of his body, even their constituent elementary particles, will themselves be ultimately squeezed out of existence.

But this picture assumes exact spherical symmetry. Because everything falls inwards to the same central point, the infinite densities and curvatures which result at that point may be argued to be atypical of a general collapse situation. Any asymmetries present in the initial state of the body would be expected to become enormously magnified as the body shrinks. Perhaps the different portions of the collapsing body would "miss" each other—even re-expand out of the black hole. For a time, it seems that hopes of this kind were entertained by various theoreticians^{23,24}. More recent work has, however, shown that within the framework of general relativity (or the Brans-Dicke theory for that matter), such hopes cannot be realized. Rigorous theorems²⁵⁻²⁷ imply that, once the matter has fallen to within a black hole, a space-time singularity of some form is inevitable—although its detailed nature may be very different from that arising in the spherically symmetrical case. (In the physical world, as opposed to mathematical models, we may take the phrase "space-time singularity" to mean a region in which space and time have become so locally distorted that the present laws of physics are no longer applicable.)

Whether or not any of the matter can conceivably ever re-emerge from a black hole region is somewhat less certain. But it could only do so if another even stranger phenomenon, a "naked singularity", occurs also. A naked space-time singularity is one which is visible to an external observer^{28,29}, unlike the one considered above (from which no signal could escape the black hole). The existence of naked singularities would present much more serious theoretical problems than singularities clothed by black holes. This is because physics at a space-time singularity is quite unknown. Extraordinary local effects (for example the production of matter out of gravitation) may be expected to occur. From the observational point of view these effects can be ignored if (and only if) information from the singularities cannot escape.

It is natural to ask, in view of such strange consequences, whether it is reasonable to suppose that matter can ever be sufficiently concentrated that a black hole develops. Might it not be that for some reason a collapsing star or superstar must always halt, or possibly reverse its collapse, before the critical size $r=r_m$ is reached? I think it is clear that although

it is likely that in some cases the collapse can be halted (if there is sufficient rotation, for example), there will also be many situations in which a point of no return is passed²⁸. In general, the larger the object or collection of objects involved, the less uncertainty there is that this point can be reached. For example, for a collection of bodies of the mass of a galaxy, it occurs at an average density less than that of air. Furthermore, this condition that a point of no return has been passed (existence of a "trapped surface"^{25,27}) is one which is stable under perturbations of the initial conditions. Thus, provided the deviations from spherical symmetry are not too great, and the collapse has proceeded sufficiently far, a black hole (or naked singularity) must result.

Rotating Black Holes

If we assume that naked singularities are absent, then a rather precise picture of the final state of a black hole may reasonably be inferred²⁸⁻³⁰. This picture is based on Kerr's solution³¹⁻³³ of the Einstein vacuum equations describing a rotating black hole. The solution depends on just two parameters m and a , where m is the mass and $maGc^{-2}$ the angular momentum of the black hole. (If an electromagnetic field is also present, one further parameter e , describing the charge, occurs³⁴.) The picture that emerges is one of an asymmetrical, possibly rotating body collapsing down past the point of no return, and producing a black hole which at first possesses asymmetries resulting from those of the body. But in a short time these asymmetries are radiated away by gravitational radiation, only the parameters a , m remaining to describe the nature of the hole. Higher moments, such as quadrupole and octupole, all then take values explicitly dependent on a and m . (This picture is supported by perturbation analysis³⁵⁻³⁹. More persuasive, however, are results within the exact Einstein theory which almost establish that a black hole which has reached a stationary state must be a Kerr solution. Israel^{40,41} showed this in the non-rotating (static) case, but required some extra conditions now effectively removed by unpublished work of H. Müller zum Hagen, D. Robinson and H. Seifert. Carter⁴² effectively obtained the result for a rotating axis-symmetric black hole, although another family of solutions disconnected from that of Kerr is not yet ruled out. Hawking has shown that any stationary black hole must be either non-rotating or axis-symmetric, thus reducing the general case to those already treated. His original argument³⁰ was based on rather too strong an assumption concerning the nature of a stationary black hole, but an improved treatment⁴³ seems to have removed this difficulty.)

Gravitational radiation is the gravitational analogue of electromagnetic radiation (light). It travels with the same speed c as does light and its existence is a theoretical consequence not only of Einstein's theory but of almost any other relativistic theory of gravitation, the chief differences being that some theories, for example the Brans-Dicke theory, allow scalar waves as well as Einstein's tensor waves.

Tensor gravitational waves have apparently been detected by Weber, but not scalar waves⁴⁴. This may be taken as some evidence against the Brans-Dicke theory, but it all depends on the mechanism by which nature produces Weber's waves. Hawking has pointed out³⁰ that in a collision between two black holes in the Brans-Dicke theory, the gravitational waves emitted are entirely tensor waves, as they are in standard general relativity. This is because the whole scalar part of the gravitational field must be radiated away (or swallowed) during the formation of a black hole in the Brans-Dicke theory, the result being a black hole identical to that of general relativity^{19,20} (that is, presumably a Kerr solution).

In view of astronomical observations that violent releases of energy are taking place in various parts of the universe (for example, quasars, explosions in galactic nuclei, radio galaxies, the source of Weber's gravitational waves) it is

reasonable to ask whether the mass-energy stored in a black hole might not in some circumstances be released to the outside world. This is not to suggest that the actual matter swallowed by the hole need in some way be released, but simply that substantial portions of the energy content of its mass be recoverable. In fact there are several processes, feasible in varying degrees, which can be invoked for energy extraction. The simplest of these is to allow black holes to coalesce and, in the process, to emit energy in the form of gravitational waves. Misner has indicated how the process of congealing a large number of black holes to a single one could, in principle, allow (proportionally) almost the entire original mass-energy to be emitted as waves²⁸. There are also methods whereby the rotational energy of a black hole may in principle be extracted. One of these^{28,45,46} is to allow a particle to fall from infinity into a region termed the "ergosphere" which lies just outside the surface of a rotating black hole. When in the ergosphere the particle has to split into two in such a way that one portion escapes to infinity possessing more mass-energy than the original particle. The other is swallowed by the black hole. If repeated many times, this process would lead to the slowing down of the rotation of the black hole and to a substantial reduction in its mass. The energy of this mass loss is recoverable (very efficiently in principle) in the kinetic energy of the final particles. (I am not suggesting that this process is likely to be important in realistic astrophysical situations, merely that if energy extraction is possible in principle, then it is conceivable that nature has found some means whereby the same ends may be achieved in fact.)

One characteristic aspect of gravitation physics is that whereas one normally finds that the extremely small size of the gravitational constant leads to an almost total insignificance of gravitational effects when compared with other forces in nature, there are sufficiently extreme situations when just the reverse is the case and the conversion of mass to energy is achieved gravitationally with an efficiency of almost 100%. It is thus worth examining any process, no matter how contrived, if it yields some hope of explaining the almost miraculous apparent efficiency of energy production in some astronomical phenomena.

A useful theoretical principle for the discussion of energy extraction from black holes is that of surface area increase. This principle has been used in various contexts^{30,45} and states that the total surface area of the black hole boundaries can never decrease (and can apparently remain constant only in a stationary situation). The boundary of a black hole (the "event horizon") is defined as a surface such that signals cannot escape from within it, but can escape from points outside it. (In the spherically symmetrical case this surface is $r=r_{\text{w}}$.) Because the surface area of a Kerr black hole is easily computed (and is $8\pi m \{m + (m^2 - a^2)^{1/2}\} G^2 c^{-2}$) this leads rapidly to several interesting inequalities. For example, there is Christodoulou's⁴⁷ concept of irreducible mass m_{ir} , given by $16\pi m_{\text{ir}}^2 = 8\pi m \{m + (m^2 - a^2)^{1/2}\}$ for a Kerr black hole, this being the minimum mass to which one could reduce the black hole by energy extraction processes. Hawking³⁰ has also used the area principle to great effect in the study of black hole collisions. If, for example, two non-rotating black holes each of mass m congeal to form a single black hole of mass M , then $M > m\sqrt{2}$. If the two come together without initially having significant relative velocity, then one can infer that an upper limit to the energy of the emitted radiation is $(2 - \sqrt{2}) mc^2$. It should be pointed out that black holes never bifurcate, they can only congeal.

Another way that black holes could be involved in energy production is in the extraction of the mass-energy content of material bodies, stars for example. The possibility of a large black hole (of 10^4 to $10^8 M_{\odot}$, say) residing at the centre of the Galaxy has often been suggested. It may be supposed that such a black hole would be continually swallowing stars.

As each star is swallowed, a certain proportion of its mass-energy would be expected to be radiated as gravitational waves. In addition, the tidal force on the star might be large enough to produce considerable "side effects" (like electromagnetic radiation and bifurcation of the star). What would happen depends a great deal on the details of the situation. Various authors have tried to use these ideas in order to explain the extraordinary observations made by Weber, which apparently imply a large flux of gravitational radiation coming from the centre of our Galaxy. This flux is so large, in fact, that if the natural assumption is made that the radiation emanates isotropically from the galactic centre, then an absurdity seems to result, namely that the Galaxy is losing mass at the rate of $2,000 M_{\odot}$ a year²¹—or perhaps even 10^5 or $10^6 M_{\odot}$ per year (P. Kafka, private communication). (At the $2,000 M_{\odot}$ a year rate, if continued, the entire Galaxy would disappear in less than 10^8 yr, a mere 1% of its present age.) Field, Rees and Sciama^{48,49} have pointed out that observations of star orbits have ruled out the possibility that such a mass loss from our Galaxy can have been continuing for anything like 10^8 yr. They argue that a loss of $70 M_{\odot}$ a year is much more in keeping with observations. In view of this discrepancy (and setting aside the possibility that the galactic centre has become active only recently—or that Weber's observations do not measure what they seem to) we are led to consider the possibility that there are gravitational waves coming from the galactic centre which are strongly beamed in the plane of the Galaxy. It may be pointed out that the Earth lies very close to the galactic plane, about 0.1% of its distance to the galactic centre⁵⁰, and in this way a mass loss of, say, as little as $10 M_{\odot}$ a year could be consistent with Weber's observations, and so consistent also with the calculations of Field, Rees and Sciama.

But what conceivable mechanism could be responsible for such beaming? An interesting suggestion by Misner (private communication) involves an "extreme" Kerr black hole, that is one for which $a=m$. Bardeen⁵¹ has suggested that such extreme black holes may occur through the accretion of matter at galactic centres, the stars being assumed to spiral gradually inwards in ever quickening (co-planar) circles. According to the Misner mechanism, these spiralling stars will beam gravitational radiation ahead of them in a small angle, in a way analogous to the electromagnetic synchrotron radiation which is produced by relativistic charged particles in electromagnetic fields. The argument is that this beaming would be sufficient not only to confine the radiation effectively to the galactic plane but also to produce the high frequency (1,660 Hz) short pulses that Weber claims to detect.

There are severe difficulties involved, to my mind, in making such a model work, but it does seem to represent a serious attempt to explain Weber's observations on the basis of accepted physical theory. As such, its consequences should be explored in full detail to ascertain the total plausibility of the idea. It may be that other suggestions involving black holes will emerge as alternative explanations of Weber's waves. On the other hand, it seems quite possible that all such explanations will eventually founder. If so, there remains the possibility that some rather different kind of gravitational catastrophe may be responsible for Weber's waves. It has long seemed to me that the presumption that the space-time singularities that arise in gravitational collapse must inevitably reside inside black holes is a product largely of wishful thinking. The possibility that naked singularities may sometimes arise must be considered seriously. Many solutions of Einstein's equations with naked singularities exist; one example is the Kerr solution with $a>m$. (This solution does not represent a black hole, being beyond the "extreme" case $a=m$.) The problem, however, is whether or not such naked singularities are likely to be self-sustaining or to occur in the collapse from a perfectly reasonable non-singular initial state. If, as might then be expected, matter production or gravitational wave production could take place

at or near such a singularity, the astrophysical consequences could be considerable. It is worth remarking, in this connexion, that a large Kerr solution with $a>m$ situated at the centre of the Galaxy would have the property that signals from the neighbourhood of its (naked) singularity are necessarily beamed in one plane⁴⁸—and this could be the galactic plane if the singularity were in some way also responsible for the very existence of the galactic plane. Of course suggestions of this sort would be hard to substantiate in the absence of a detailed theory of singularities. But if all black-hole explanations fail, it may be that we shall be driven to consider possibilities of this kind.

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Measurements of Lunar Magnetic Field Interaction with the Solar Wind

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The remanent magnetic field at the lunar surface is compressed as much as 40% above its initial value by the solar wind, but the total remanent magnetic pressure is less than the stagnation pressure by a factor of six, implying that a local shock is not formed.

THIS article reports a study of the compression of the remanent lunar magnetic field by the solar wind¹, based on measurements of remanent magnetic fields at four Apollo landing sites²⁻⁵, and of the solar wind at two of these sites⁶⁻⁷. Measurements at the Apollo 12 site show, to first order, a compression of the remanent field in direct proportion to the solar wind pressure.

Discussion of Interaction

The interaction of a planetary sized body with the solar wind plasma depends on the electromagnetic properties of that body, and in the case of the Earth the terrestrial field is compressed on the sunward side to a point where the magnetic and plasma pressures balance; the Earth's magnetosphere acts as a barrier to the plasma flow, causing a shock front to be formed as shown in Fig. 1 (refs. 8-11). For planets with magnetic fields much weaker than that of the Earth, the interaction may be dominated by the properties of the planetary ionosphere—such may be the case for Venus and Mars^{12,13}.

The Moon has neither sufficient ionosphere nor a global permanent magnetic field large enough to deflect the solar wind, so no large-scale shock front and magnetosheath are seen¹⁴⁻¹⁶. But magnetic concentrations ("magcons"¹⁷) in the lunar surface could, if of sufficient extent and field strength, interact locally with the solar wind when the magcons are on the daytime lunar side. Remanent magnetic fields of 38 gammas have been measured at the Apollo 12 site³, 43 and 103

gammas at two Apollo 14 sites⁴, and 6 gammas at the Apollo 15 site⁵; the Apollo 12 and 14 field magnitudes are adequate to deflect the solar wind if the field sources are of sufficient size, the critical size being approximated¹⁷ by the interaction region thickness $L_0 = Ac/\omega_p$, where c is the speed of light, ω_p is the electron gyrofrequency, and $A \lesssim 5$; for typical solar wind conditions $L_0 \lesssim 10$ km. If the field source scale size is $L \ll L_0$, the field would be essentially undistorted by the solar plasma; if $L \gg L_0$, the field could be compressed, causing deflexion of the solar wind and possible formation of a local shock (D. L. Siscoe and B. Goldstein, unpublished work). For intermediate scale sizes $L \gtrsim L_0$, some field compression and plasma deflexion could occur, but not necessarily enough to set up a shock (see Fig. 2).

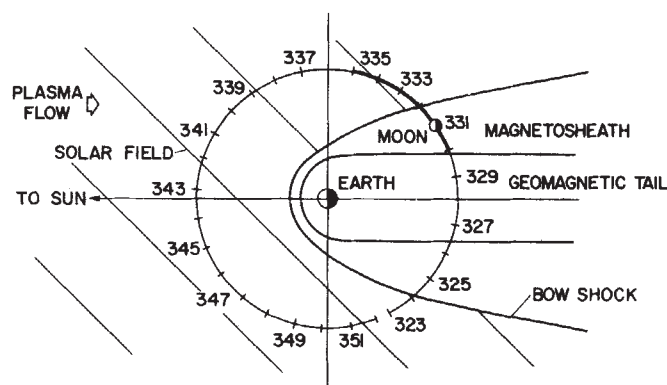


Fig. 1 Lunar orbit projection in the solar ecliptic plane during the first post-deployment lunation, 1969. Apollo 12 daylight data discussed in this article were obtained in the enhanced segment of the orbit.

We have examined simultaneous magnetic field and solar plasma data during daylight times at the Apollo 12 site. During these times the electromagnetic environment of the Moon varies strongly with lunar orbital position (see Fig. 1);

the electromagnetic properties of the geomagnetic tail, magnetosheath, and free-streaming solar wind are distinct and cause different responses by the Moon. The total magnetic field at the lunar surface will in general be the vector sum of the external field, permanent and induced lunar fields, and Moon-plasma interaction fields:

$$\mathbf{B}_A = \mathbf{B}_E + \mathbf{B}_S + \mathbf{B}_P + \mathbf{B}_T + \mathbf{B}_\mu + \mathbf{B}_D + \mathbf{B}_F \quad (1)$$

Here $\mathbf{B}_A$ is the total surface magnetic field, measured by the Apollo 12 lunar surface magnetometer¹⁸; $\mathbf{B}_E$ is the extralunar (solar or terrestrial) driving magnetic field, measured by the lunar-orbiting Explorer 35 magnetometer¹⁹; $\mathbf{B}_S$ is the steady remanent field at the site due to magnetized material; $\mathbf{B}_P$ is the poloidal field (TE mode) corresponding to eddy currents induced in the lunar interior by the time changing external field; $\mathbf{B}_T$ is the toroidal field (TM mode) corresponding to unipolar currents driven through the Moon by the plasma motional $\mathbf{V} \times \mathbf{B}_E$ electric field; $\mathbf{B}_\mu$ is the field induced in lunar permeable material; $\mathbf{B}_D$ is the field due to plasma diamagnetism in the lunar cavity; and $\mathbf{B}_F$ is the interaction field associated with the hydromagnetic solar wind flow past the Moon. $\mathbf{B}_F$ contains the compression field discussed in this article.

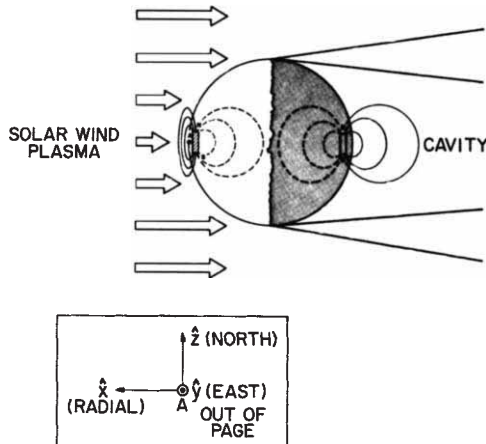


Fig. 2 Compression of a local remanent magnetic field by a high density solar wind plasma. The remanent field is unperturbed during nighttime (antisolar side), whereas on the sunlit side it is compressed. Inset shows the coordinate system, with origin at point A, which will be used in this paper.

The fields comprising the right hand side of equation (1) can vary in relative magnitude depending on such factors as driving field frequency, lunar orbital position, location on the lunar surface, and solar activity; furthermore, some of the field contributions can be neglected in the proper conditions. We neglect the diamagnetic cavity field $\mathbf{B}_D$ because all data considered in this article are obtained while the surface magnetometer is on the sunlit side of the Moon. As the global relative magnetic permeability μ/μ_0 has been determined²⁰ to be 1.03 ± 0.13 , the upper limit for the induced magnetization field is calculated to be 0.4 gammas (only twice the Apollo 12 magnetometer reduction of 0.2 gamma) for the maximum measured external field $\mathbf{B}_E = 18$ gammas and therefore $\mathbf{B}_\mu$ is neglected.

Next we consider the toroidal field $\mathbf{B}_T$. This field mode has cylindrical symmetry on a global scale and would be measured during both daytime and nighttime at the Apollo 12 site; however, no appreciable toroidal field has been found in nighttime analyses²⁰. The daytime data presented here also show no evidence for a strong toroidal field. The toroidal field would be produced by unipolar currents driven through the Moon by the $\mathbf{V} \times \mathbf{B}_E$ electric field, so $\mathbf{B}_T$ should be proportional to solar wind velocity $\mathbf{V}$ but not to density. Such a relationship between field and velocity is not seen. Furthermore, as the average solar wind vector quantities $\mathbf{V}$ and $\mathbf{B}_E$

generally lie in the solar ecliptic plane, the electric field is on the average directed normal to the ecliptic and thus a global toroidal field would also most likely be directed in the ecliptic plane^{21,22}, that is, maximized along the lunar equator in the easterly direction and minimized along the northerly direction. The external field $\mathbf{B}_E$ changes polarity several times in an 18 h period covering days 330–331, but the corresponding polarity switch in the easterly component of $\mathbf{B}_T$, that would necessarily occur along with a $\mathbf{B}_E$ change, is not seen; the largest effect occurs in the northerly component, and so we neglect the toroidal term $\mathbf{B}_T$.

Equation (1) may therefore be rewritten:

$$\Delta\mathbf{B} = \mathbf{B}_A - (\mathbf{B}_E + \mathbf{B}_S) = \mathbf{B}_P + \mathbf{B}_F \quad (2)$$

This form is convenient because $\Delta\mathbf{B}$ is a combination of the two fields that are measurable as functions of time and the third field, $\mathbf{B}_S$, is a constant (38 gammas).

Now we consider the terms $\mathbf{B}_P$ and $\mathbf{B}_F$ in equation (2). The poloidal field $\mathbf{B}_P$ has been found to be the dominant induction mode for both nighttime transient analysis^{20,23,24} and daytime harmonic analysis^{25,26} of lunar magnetometer data and there-

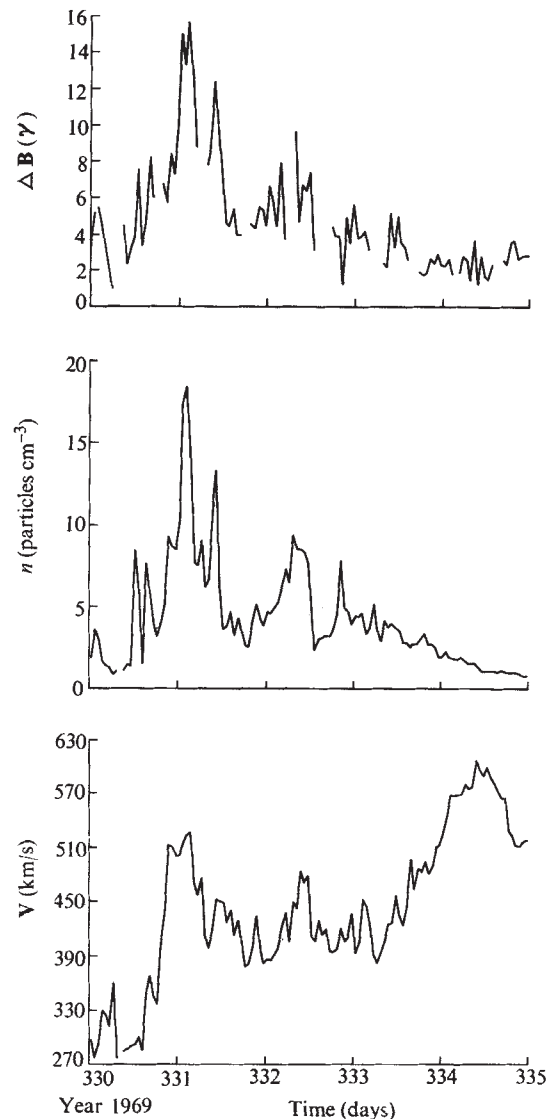


Fig. 3 Simultaneous graphs of magnitude of the vector $\Delta\mathbf{B} = \mathbf{B}_A - (\mathbf{B}_E + \mathbf{B}_S)$, plasma proton density and plasma velocity. $\mathbf{B}_A$ is the total surface field measured by the Apollo 12 lunar surface magnetometer, $\mathbf{B}_E$ is the extralunar field measured by lunar orbiting Explorer 35, and $\mathbf{B}_S$ is the remanent field at the Apollo 12 site. Orbital position of the Moon during days 330–335 is shown in Fig. 1.

fore must be considered in the general case. Because the eddy current induction mode $\mathbf{B}_P$ is proportional to the time rate of change of the external driving field $\mathbf{B}_E$, $\mathbf{B}_P$ can be neglected for low frequencies^{21,22} below about 3×10^{-4} Hz (ref. 25) but not for high frequencies. Equation (2) can therefore be written in the following two forms applicable to lunar daytime data:

$$\text{for high frequencies } (> 3 \times 10^{-4} \text{ Hz}) \Delta \mathbf{B} = \mathbf{B}_P + \mathbf{B}_F \quad (3)$$

$$\text{for low frequencies } (< 3 \times 10^{-4} \text{ Hz}) \Delta \mathbf{B} \rightarrow \mathbf{B}_F \quad (4)$$

Magnetic Field and Plasma Measurements

According to equation (4), we can investigate the plasma interaction field $\mathbf{B}_F$ by using low frequency daytime data. Fig. 3 shows simultaneous one hour average plots of the magnitude of the vector field difference $\Delta \mathbf{B} = \mathbf{B}_A - (\mathbf{B}_E + \mathbf{B}_S)$, solar wind proton density, and solar wind velocity magnitude measured at the Apollo 12 site. The time scale on Fig. 3 corresponds to the orbital region shown in Fig. 1 and includes data from the magnetosheath and free-streaming solar wind. All data are expressed in the surface coordinate system ($\hat{x}$, $\hat{y}$, $\hat{z}$)

which has its origin at the Apollo 12 magnetometer site; $\hat{x}$ is directed radially outward from the surface while $\hat{y}$ and $\hat{z}$ are tangent to the surface, directed eastward and northward, respectively. Components of the steady remanent field at the Apollo 12 site have been determined¹⁸ to be $B_{sx} = -24.4 \gamma$, $B_{sy} = +13.0 \gamma$ and $B_{sz} = -25.6 \gamma$. By inspection we see a strong relationship between the magnitude ΔB and plasma proton density (n); no such strong correlation, however, is apparent between ΔB and velocity V alone.

Fig. 4 shows the x (vertical), y (easterly), and z (northerly) components of $\Delta \mathbf{B}$. Correlation with density is seen in all three components, but it is stronger in the horizontal components y and z and strongest in the z direction. We note that each component field change with plasma density generally has the same polarity as each remanent field component (B_{sx} and B_{sz} are negative and B_{sy} is positive). The correlations between the field difference components ΔB_i and plasma proton density n suggest that the field change $\Delta \mathbf{B}$ is due to a compression of the local remanent field $\mathbf{B}_S$ by the solar wind, with the largest compression occurring in the z -component. This preferential compression of the z -component may result from the geometric configuration of the remanent field.

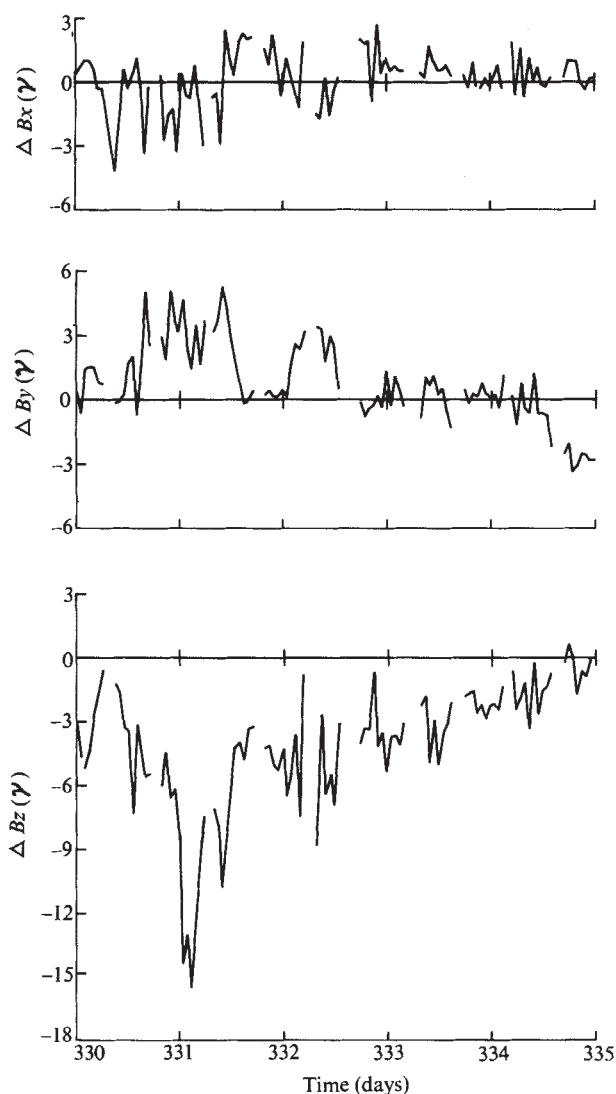


Fig. 4 Components of the magnetic field difference vector $\Delta \mathbf{B}$. Data are expressed in the surface coordinate system ($\hat{x}$, $\hat{y}$, $\hat{z}$) which has its origin at the Apollo 12 magnetometer site; $\hat{x}$ is directed radially outward from the surface while $\hat{y}$ and $\hat{z}$ are tangent to the surface, directed eastward and northward, respectively. The unperturbed steady remanent field at the Apollo 12 site is $\mathbf{B}_S = (-24.4 \gamma, +13.0 \gamma, -25.6 \gamma)$.

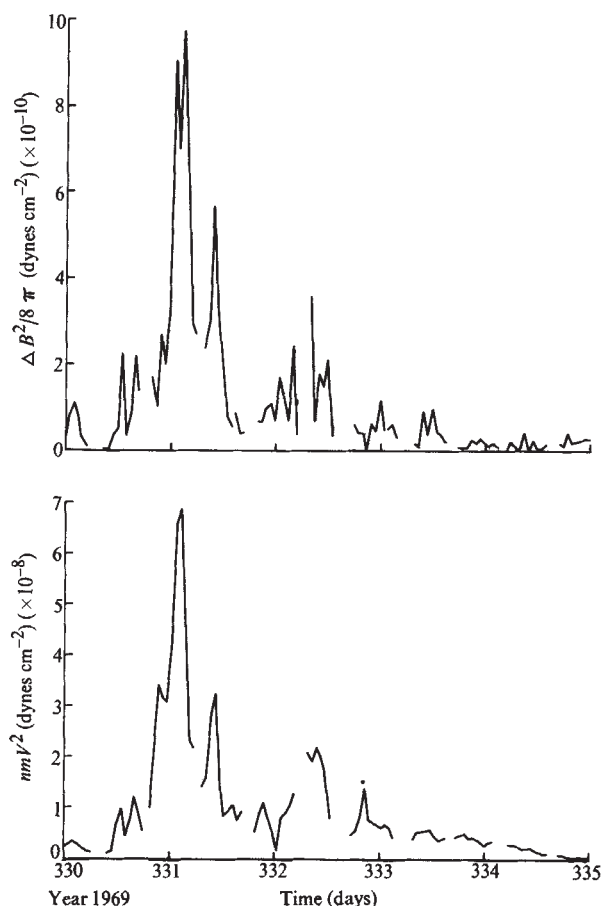


Fig. 5 Simultaneous plots of the magnetic field pressure difference $\Delta B^2/8\pi$ and solar wind pressure at the Apollo 12 surface site, showing a correlation between the pressures.

If in the low frequency case $\Delta \mathbf{B}$ is indeed a field change due to compression of the local remanent field, then the magnetic field and plasma pressures should be related. Simultaneous plots of the magnetic pressure change $\Delta B^2/8\pi$ and plasma pressure nmV^2 (n is proton density and m is proton mass) are shown in Fig. 5; a correlation between magnetic and plasma pressures is readily seen. The nature of the correlation is illustrated more clearly in Fig. 6, which contains the data of Fig. 5 plus data from the same orbital positions in the

succeeding lunation (days 359 to 365). The pressures are related throughout the measurement range; fitting the data averages by a least squares straight line, we calculate a slope $K \approx 0.01$, which is approximately the ratio of magnetic pressure change to plasma pressure.

The ratio of plasma pressure to total magnetic pressure is expressed

$$\beta = \frac{nmV^2}{B_{ST}^2/8\pi} \quad (5)$$

where $B_{ST} = B_S + \Delta B$ is the total surface compressed field. During times of maximum plasma pressure shown in Fig. 5, we calculate $\beta = 5.9$; $\beta \leq 1$ would imply that the field had been compressed to the stagnation magnitude required to stand off the solar wind and possibly form a local shock. Compression of the remanent field alone therefore does not cause the stagnation condition to be reached during the time period of these data; however, at high frequencies the induced poloidal field B_P is also compressed ($\Delta B = B_P + B_F$ in equation (3)), and thus it is possible that the stagnation pressure is reached for short time periods. Total surface fields of over 100 gammas have been observed² when large solar field transients pass the Moon; therefore a shock could be formed temporarily at the Apollo 12 site (as well as at the Apollo 14 site).

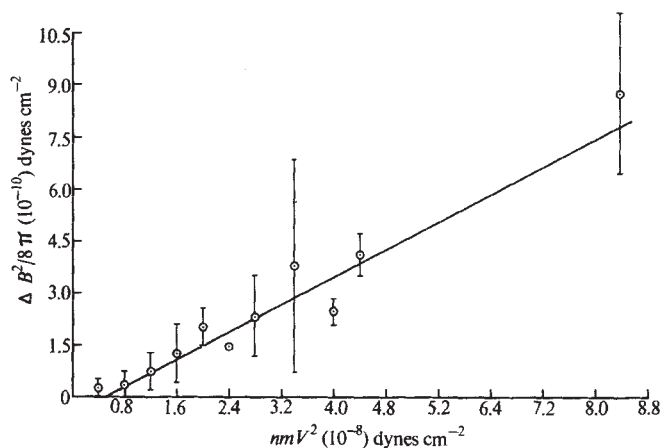


Fig. 6 Magnetic field pressure difference versus solar wind plasma pressure at the Apollo 12 site.

If the Apollo 12 field were assumed to be due to a single dipolar source, then Explorer 35 measurements would constrain its size³ to $L < 200$ km. As the field does interact with the solar wind, its scale length¹⁷ $L \gtrsim 2$ km; thus a single dipolar Apollo 12 magcon is probably in the size range $2 \text{ km} \lesssim L < 200$ km. But, in the Apollo 14 region, 180 km distant from the Apollo 12 site, two field values of 43 and 103 gammas have been measured at sites 1.1 km apart. It is therefore possible that the field at Apollo 12 is due to a magcon which is not a single dipolar source, but rather is an extended source which is nonuniformly magnetized such that its field intensity varies strongly with position. Perhaps a subsurface layer of material was uniformly magnetized during solidification, and was later altered by tectonic activity or fracturing and shock demagnetization by meteorite impacts.

Implications for Conductivity Calculations

We have shown that the remanent magnetic field at the Apollo 12 site is of sufficient magnitude and extent to interact

with the impinging solar wind plasma, compressing the remanent field as much as 40%. The interaction region involves a surface field of unknown geometrical configuration which may generate substantial plasma currents in preferred directions, possibly generating plasma noise over a wide frequency range. When lunar daytime magnetometer data are used to study whole Moon properties therefore, knowledge of simultaneous solar wind properties is important.

Two different approaches have been used to calculate the internal lunar electrical conductivity profile from Apollo 12 lunar surface magnetometer data. The first approach involves a transient response analysis of measurements made during times that the surface magnetometer was on the antisolar (nighttime) side of the Moon^{20,23,24}. The second involves Fourier harmonic analysis of measurements made on the sunlit (daytime) side of the Moon^{25,26} where the solar plasma interacts with the remanent field and simultaneously with the poloidal field induced in the Moon. The harmonic analysis yields two different conductivity profiles, one calculated from y -axis (easterly) data alone and the other from z -axis (northerly) data alone; this y - z asymmetry is not evident in the transient analysis.

The y - z asymmetry can be explained by considering the effect of remanent field compression by the solar wind. In the harmonic analysis the transfer functions $A_i(f) = b(f)_{Ai}/b(f)_{Ei}$, where $i = x, y, z$ and $b(f)_i$ are the Fourier transformed values of the time series magnetic fields B_i . The total surface field is assumed to be the sum of only the external driving field and the poloidal (TE) lunar response mode, so that $B_{Ai} = B_{Ei} + B_{Pi}$. In this case, spherical symmetry requires that the two horizontal field transfer functions A_z and A_y be equal; however, the harmonic analysis calculations yield $A_z > A_y$ for all measured frequencies.

If remanent field compression is considered, then the transfer functions calculated in the harmonic analysis are actually $A_i(f) = (b_{Ei} + b_{Pi} + \Delta b_i)/b_{Ei}$. We see in Fig. 4 that $\Delta B_z > \Delta B_y$, which would cause $A_z > A_y$ at low frequencies. If the Fourier analysed B_{Ai} data could be corrected for the plasma interaction with the remanent field, the "adjusted" A_y and A_z profiles (with Δb_i removed) would tend toward coincidence and both would lie below the published^{25,26} harmonic A_y curve. These adjusted transfer functions A_y and A_z would in turn alter the lunar electrical conductivity profile calculated by harmonic analysis of daytime magnetometer data.

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Definition and Antagonism of Histamine H₂-receptors

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H₂-receptor antagonist, a new group of drugs, may help to unravel the physiology of histamine and gastrin.

HISTAMINE stimulates the contraction of smooth muscle from various organs, such as the gut and bronchi, and this effect can be suppressed by low concentrations of mepyramine—a typical antihistaminic drug. The pharmacological receptors involved in these mepyramine-sensitive histamine responses have been defined as H₁-receptors¹. Histamine also stimulates the secretion of acid by the stomach², increases the heart rate³ and inhibits contractions in the rat uterus⁴; these actions cannot be antagonized by mepyramine and related drugs. This article is concerned with the classification and specific blockade of the receptors involved in mepyramine-insensitive, non-H₁, histamine responses. Work was started in 1964, based on a simple analogy with catecholamine β -receptors and their antagonists and on the structure of histamine. Since then about 700 compounds have been synthesized and tested.

Identification of H₂-receptors

Quantitative histamine responses in five tissue systems have been used to assay agonist and antagonist activity of new compounds. Three non-H₁ systems were used: gastric acid secretion measured by the pH of the lumen-perfusate of an anaesthetized rat; the contraction frequency of an isolated piece of guinea-pig right atrium; and the contractions, electrically evoked at 1 min intervals, of an isolated piece of rat uterine horn—both of these isolated tissues were suspended in oxygenated McEwen's solution at 34° C. Two H₁-receptor systems were also used: the contractions of an isolated piece of guinea-pig terminal ileum suspended in oxygenated Tyrode solution at 37° C, and the contractions of the body of the

stomach of an anaesthetized rat measured from pressure changes in an intragastric balloon.

The relative agonist activity of each of a series of methyl derivatives of histamine was estimated on both guinea-pig ileum (H₁) and guinea-pig atrium (non-H₁). Fig. 1 shows that these two assays gave indistinguishable estimates of the relative activities of N-methylhistamine, N,N-dimethylhistamine, α -methylhistamine and β -methylhistamine. Methyl substitution on either of the ring nitrogen atoms, namely 1- and 3-methylhistamine, produced more or less inactive compounds, and there were no significant differences in the estimates of relative activity obtained from the ileal and atrial assays. 4-Methylhistamine, however, had 43.0 (39.8–46.5)% of the activity of histamine when assayed on the atrium but only 0.23 (0.20–0.27)% when assayed on the ileum; the difference between these estimates is highly significant. Conversely, 2-methylhistamine had a relative activity of 4.4 (4.1–4.8)% on the atrium but 16.5 (15.1–18.1)% on the ileum: again, this is a significant difference.

Differences between the ileal and atrial assays and between 2- and 4-methylhistamine were tested for general validity by extending the measurements to uterine muscle *in vitro* (non-H₁) and to gastric motility (H₁) and gastric acid secretion (non-H₁) *in vivo*. The mean relative activities of the two compounds, estimated on each of the five tissue systems, are given in Table 1. The assays have been arranged for comparison into H₁ and non-H₁ groups and the results have been analysed by calculating heterogeneity χ^2 values. The analysis of χ^2 for 4-methylhistamine shows that the contribution to total heterogeneity from differences between the two groups of assays is very significantly greater than the contribution from differences within the two groups or from within assays. The significant "within groups" heterogeneity for 4-methylhistamine is almost wholly attributable to the relatively low estimate of activity on rat uterus. Similarly, with 2-methylhistamine the greatest contribution to the heterogeneity χ^2 comes from the "between-groups" differences. The significant "within groups" heterogeneity for 2-methylhistamine is almost totally due to the

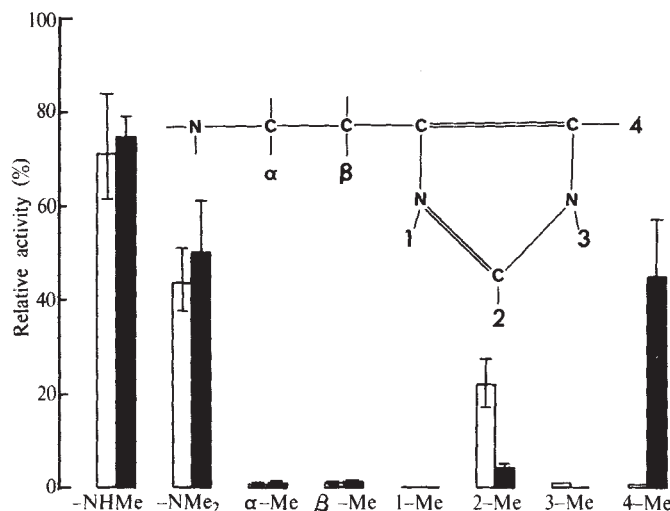


Fig. 1 Bar chart showing activity of histamine derivatives, relative to histamine (=100), estimated on both ileum (white columns) and atrium (hatched columns). Each bar gives mean relative activity (with 95% confidence limits) from pooling results of several valid assays. Each assay, using a different piece of tissue, was based on a 2+2 randomized block design. Nomenclature of the derivatives follows from the system, customary for histidine⁵, in which (a) the ring nitrogen adjacent to the side-chain is named position 1 and the second ring nitrogen becomes position 3, and (b) the carbon atom adjacent to the side-chain nitrogen is called the α -position.

relatively high estimate of activity on the atrial assay. The absence of a clear pattern to the "within groups" heterogeneity for these two compounds makes it unlikely that a further subdivision of the non- H_1 group is necessary. For both compounds, the outstanding feature is the very significant difference between the H_1 and non- H_1 groups of assays. Results for the histamine analogue, 3-(2-aminoethyl)-1,2,4-triazole, are included in Table 1 for reference. The χ^2 for heterogeneity "within assays" is significant for this compound, and is largely due to one very low value in the atrial assays; otherwise the

heterogeneity "between groups" or "within groups" was not significant, as shown by the variance ratios.

The assay results on the triazole analogue of histamine show that it is not inherent in the five test systems that they should give estimates of relative activity that differ by more than normal experimental and sampling errors. The significant "between groups" differences for the 2 and 4-methylhistamines are thus not likely to be due to tissue differences alone. Differences in the properties of histamine and these derivatives were therefore sought in other tests. Estimates of the pA_2 for mepyramine using each of the agonists on guinea-pig ileum were found to be indistinguishable; from this it has been assumed that each of the agonists acts on the same set of histamine receptors⁷.

Complete dose-response curves for each agonist were measured on all test systems except gastric motility. No significant differences were found among them in the "slope" of the dose-response curves or in the level of maximum responses. Finally, similar time-courses of onset and offset of effect were found on all tissues. These properties are expected if the differences in the activities of the compounds are due to differences in drug-receptor interactions rather than to differences in access, metabolism or efficacy⁸. The estimated relative activities might then be some function of the ratio of the corresponding affinity constants and, if so, would identify a homogeneous population of receptors in the three non- H_1 systems. Provisionally these will be identified as H_2 -receptors.

H_2 -receptor Antagonists

All compounds were tested for ability to inhibit histamine-stimulated gastric secretion in anaesthetized rats on the assumption that if H_2 -receptor antagonists were to be found it seemed reasonable to expect the inhibition. It was certain, however, that other types of inhibitor of gastric secretion could also be picked up by this test. Consequently, quantitative analysis on isolated tissue systems has been used to filter out inhibitors of gastric secretion which failed to show specific antagonism to histamine.

By considering the effect of structural change on activity of compounds in the screening test we progressed to N-methyl-N'-(4-(4(5)-imidazolyl)butyl)thiourea (this compound is the

Table 1 Activities Relative to Histamine (=100)

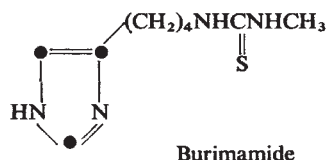
	H_1 group		Non- H_1 group			Source of variation	Statistical analysis				
	Guinea-pig ileum <i>in vitro</i>	Rat stomach contractions <i>in vivo</i>	Guinea-pig atrium <i>in vitro</i>	Rat uterus <i>in vitro</i>	Rat gastric acid secretion <i>in vivo</i>		DF	χ^2	MS	F	P
4-Methyl-histamine	0.2	0.3	43.0	25.3	38.9	Within assays	4	3.15	0.79	—	NS
						Within groups	3	39.56	13.19	16.7	0.01
						Between groups	1	6,350.96	6,350.96	481.6	0.001
2-Methyl-histamine	16.5	18.6	4.4	2.1	2.0	Within assays	5	5.38	1.08	—	NS
						Within groups	3	76.19	25.38	23.6	0.01
						Between groups	1	728.42	728.42	28.7	0.05
3-(2-Amino-ethyl)-1,2,4-triazole	12.7	10.5	6.8	9.5	13.7	Within assays	4	49.62	12.41	—	0.001
						Within groups	3	96.59	32.20	2.60	NS
						Between groups	1	46.61	46.61	1.45	NS

The results of individual assays were analysed by calculating heterogeneity χ^2 values for each of three separate contrasts: "Within assays", heterogeneity due to differences between individual, replicated assays on any one test system; "within groups", heterogeneity due to differences in mean relative activities within either the H_1 or non- H_1 group of assays, and "between groups", heterogeneity due to differences between the two groups of assays treated as a whole. The tests of significance were done as described by Finney⁶; mean squares

$$\left(MS = \frac{\chi^2}{DF} \right)$$

were calculated for each source of variation (SV), then each SV was compared with the one immediately above it in the table using the variance ratio (F) test.

subject of British patent applications 52891/69, 49007/70, 30834/70 and 2918/71):



The remainder of this article describes some of the pharmacological properties of burimamide.

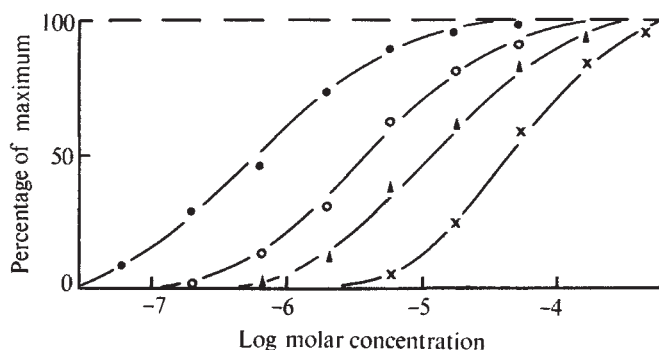


Fig. 2 Histamine cumulative log-dose response curves from guinea-pig atrium: without antagonist (●) and after equilibration with burimamide 2×10^{-5} M (○), 4×10^{-5} M (▲) and 2.7×10^{-4} M (×). Using Marquardt's algorithm⁹ for non-linear least-squares curve-fitting, each dose-response curve could be fitted to the logistic function¹⁰

$$y = \frac{Y \cdot c^n}{c^n + K^n}$$

where y =response and Y =maximum response in same units; c =drug concentration giving response y and K =ED₅₀, the drug concentration for 0.5 Y response; numerical parameter n =function of slope of log dose-response curve at ED₅₀ level (=1 in rectangular hyperbola).

The antagonism of histamine by burimamide on isolated guinea-pig atria, estimated from displacement of dose-response curves, has been analysed as shown in Figs. 2 and 3. The time-cycle needed to complete each cumulative dose-response curve varied between 45 and 60 min. Combination of this long time-cycle and problems associated with washout of antagonists imposed severe restrictions on experimental design and an ideal solution was not found. Experiments such as that illustrated in Fig. 2, however, seem satisfactory. This shows that burimamide produced a dose-related displacement of histamine dose-response curves without significantly affecting their "slope" or maximum. Although some variation in the shape of individual curves was seen in other experiments, analysis of the variance of the parameters n and Y , derived from curve-fitting, showed that in the dose range studied burimamide did not produce statistically significant dose-related changes in the "slope" or maximum of the histamine dose-response curves. The slope and 95% confidence limits for the regression of $\log (DR-1)$ on $\log (B)$ were 0.98 (0.90–1.06) and this is not significantly different from unity. Analysis of variance showed that the sum of squares, attributable to a quadratic component in the regression, was insignificant. Burimamide is thus not only a surmountable antagonist of histamine on atria, it also meets the conditions—namely parallel displacement of dose-response curves and a linear relation between concentration of antagonist and $(DR-1)$ —for this antagonism to be due to competition with histamine for a common site. The putative drug-receptor complex can now be characterized by an (apparent) dissociation constant (K_B) found by evaluating the regression equation for a dose-

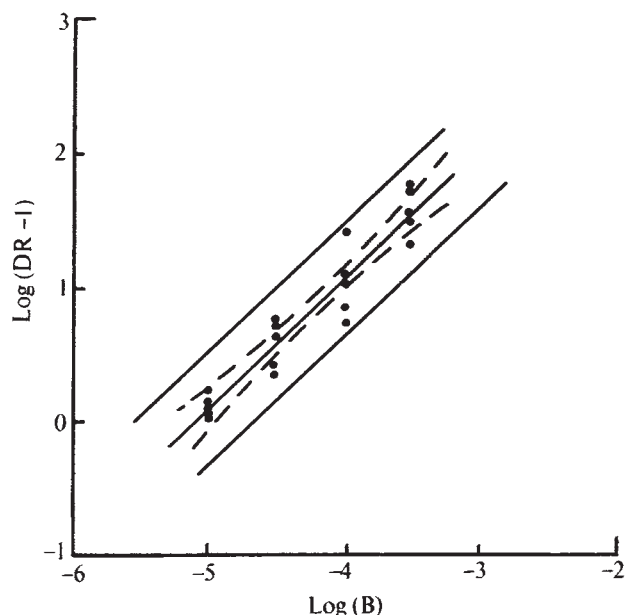


Fig. 3 Antagonism of histamine by burimamide on guinea-pig atrium. Antagonism is expressed by histamine dose-ratios (DR) needed for equal responses before and after burimamide (B) equilibration. If burimamide and histamine compete for a common site (and certain assumptions hold) then $\log (DR-1) = \log (B) - \log K_B$, where K_B =(apparent) dissociation constant for the antagonist-receptor interaction¹¹; the data are plotted to test this relationship. Each DR was calculated from the ratio of ED₅₀ values estimated from fitting a logistic function to each of a separate pair of dose-response curves. Twenty pairs of dose-response curves were obtained from eleven tissue preparations. Concentrations of burimamide were 1×10^{-5} M, 3×10^{-5} M, 1×10^{-4} M and 3×10^{-4} M. Regression of $\log (DR-1)$ on $\log (B)$ was calculated by method of least squares and 95% confidence limits for the regression (dashed lines) and for a single estimation (continuous lines) are shown. K_B (apparent)= 7.8×10^{-6} M (6.4–9.6); pA_2 =5.11 (5.02–5.19). Slope=0.98 (0.90–1.06).

ratio of 2. As Fig. 4 shows, the value of K_B for burimamide on atria was estimated to be 7.8 (6.4 – 9.6) $\times 10^{-6}$ M. This corresponds to an empirical pA_2 of 5.11 (5.02–5.19).

Estimates of the apparent K_B for burimamide on atria have also been made using 2 and 4-methylhistamine as agonists. As Table 2 shows, although the activities of these agonists are significantly different from each other, the corresponding estimates of the K_B for burimamide are not. The regression in Fig. 3, which can be derived theoretically as the general case for competition between agonist and antagonist, contains no constants for the agonist, and so predicts that an estimate of the antagonist K_B will be independent of the equilibrium constant for the agonist which has been used⁷. The results in Table 2 are consistent with this prediction, and increase the evidence that burimamide is a competitive antagonist of histamine on atria.

Evidence that the agonist activity ratios of some histamine derivatives were apparently homologous on both guinea-pig atrium and rat uterus has already been used to argue that the histamine receptors on these two tissues are homogeneous. They were provisionally defined as H₂-receptors. When the interaction between burimamide and histamine on rat uterus was studied in the same way as for guinea-pig atrium, very similar results were found. The histamine dose-response curves were displaced without change in maximum or "slope". The regression between $\log (DR-1)$ and $\log (B)$ was found to be linear with a slope of 0.96 (0.80–1.12) and the estimated apparent K_B was 6.6 (4.9 – 8.3) $\times 10^{-6}$ M which is equivalent to a pA_2 of 5.17 (5.08–5.30). On rat uterus, as on guinea-pig atrium, burimamide acts like a competitive antagonist of histamine. Since the estimated K_B is not significantly different from that found on atrium this defines the homogeneity of the

two populations of receptors, H_2 -receptors, and allows burimamide to be defined as an H_2 -receptor antagonist⁷.

The specificity of this histamine antagonism was examined by testing for an interaction between burimamide and isoprenaline. Like histamine, isoprenaline stimulates guinea-pig atrium and inhibits rat uterus, but it does so by acting on catecholamine β -receptors. Burimamide, in concentrations up to 8×10^{-4} M, failed to displace isoprenaline dose-response curves significantly on either tissue.

Table 2 Dissociation Constant (K_B) for Burimamide estimated on Guinea-pig Ileum using Three Agonists

	Agonist $ED_{50}/$ 10^{-6} M With 95% confidence limits	Burimamide $K_B/$ 10^{-6} M With 95% confidence limits
Histamine	1.1 (0.9–1.4)	7.8 (6.4–9.6)
4-Methylhistamine	3.1 (2.0–4.3)	7.2 (5.2–9.2)
2-Methylhistamine	19.8 (9.7–29.9)	6.9 (5.7–8.2)

Activities of each agonist are expressed as ED_{50} values obtained from fitting the logistic function to complete dose-response curves.

Table 3 Burimamide Antagonism on Isolated Tissues

Tissue	Agonist	Slope of log (DR-1) on log (B) regression With 95% confidence limits	Burimamide $K_B/$ 10^{-6} M With 95% confidence limits
Atrium	Histamine	0.98 (0.90–1.06)	7.8 (6.4–9.6)
Uterus	Histamine	0.96 (0.80–1.12)	6.6 (4.9–8.3)
Ileum	Histamine	1.32 (1.11–1.54)	288 (95–870)
Ileum	Carbachol	1.44 (1.16–1.72)	174 (60–500)

Finally, the specificity of burimamide antagonism was examined on guinea-pig ileum where the histamine responses are mediated by H_1 -receptors. When large enough doses of burimamide were used, the ileal contractions produced by either histamine or carbachol could be suppressed. The slope of the regression of log (DR-1) on log (B), and the corresponding estimate of an apparent K_B , are shown in Table 3. Comparable results for the burimamide/histamine interactions on both atrium and uterus have been included. The slopes of the regressions for burimamide on ileum are significantly different from unity, but are not significantly different from each other. The apparent K_B estimated for both histamine and carbachol with each agonist is very much larger than that found on the H_2 -receptor systems and the two estimates are not significantly different. These results on ileum are not consistent with competitive antagonism but they are consistent with some other non-specific depressant action, perhaps on the contractile system.

In summary, burimamide is a specific competitive antagonist of H_2 -receptors; no significant interaction with catecholamine β -receptors, histamine H_1 -receptors or acetylcholine (muscarinic) receptors was found at the concentrations studied.

Histamine Receptors and Mammalian Gastric Secretion

In routine experiments in anaesthetized rats, potential inhibitors were given by rapid intravenous injection during the plateau of gastric acid secretion produced by continuous intravenous infusion of histamine. The degree of inhibition which an antagonist can produce in experiments like this depends on the pre-dose level of secretion in relation to the secretory maximum. Since it was impractical to estimate the maximum secretory response for each rat individually, an average complete dose-response curve at the steady state to

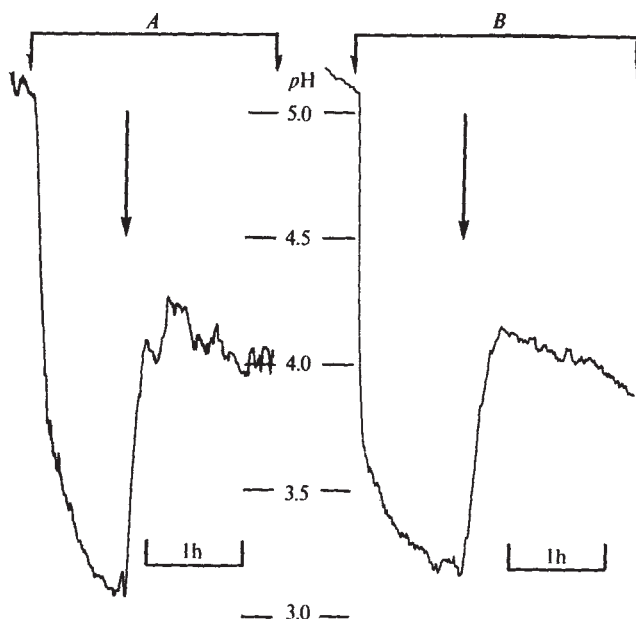


Fig. 4 Rat gastric acid secretion estimated by pH of lumen-perfusate. Anaesthetic: urethane. Perfusion rate: 3 ml. min^{-1} . **A**, Continuous infusion of histamine ($2.5 \times 10^{-7} \text{ mol kg}^{-1} \text{ min}^{-1}$ intravenously) evoked acid secretion and reduced the pH to 3.1 in 1 h. Injection (arrow) of burimamide ($6.4 \times 10^{-5} \text{ mol kg}^{-1}$ intravenously) rapidly raised the pH to more than 4.1, which is equivalent to about 90% inhibition of acid output from the stomach. **B**, As in **A** but secretion stimulated by pentagastrin ($1 \times 10^{-6} \text{ g kg}^{-1} \text{ min}^{-1}$ intravenously).

different rates of infusion of histamine was established in twelve rats. This showed that an infusion of $2.5 \times 10^{-7} \text{ mol kg}^{-1} \text{ min}^{-1}$ of histamine produced a mean of 70% of the maximum response. This rate of infusion was used in subsequent experiments. The inhibitory response to a single intravenous injection of burimamide in one of these experiments is shown in Fig. 4A; the inhibition typically reached a maximum in less than 30 min and recovered with a half-time between 1.5 and 3.0 h. The dose-response relationship for this inhibition was measured in thirty rats and the ED_{50} was found to be $6.1 \times 10^{-6} \text{ mol kg}^{-1}$. In another experiment, burimamide $1 \times 10^{-5} \text{ mol kg}^{-1}$ was given intravenously to fifteen rats during the steady state secretion produced by each of three rates of histamine infusion. Two dose-response curves were plotted; the control curve was the secretory response immediately before the injection of antagonist and the second curve was the secretory level at maximal inhibition. The dose-response curves were found to be linear, parallel and displaced by a dose-ratio of 2.6. Burimamide is thus an effective, surmountable inhibitor of histamine-stimulated gastric secretion in anaesthetized rats but this is no basis for assuming that the inhibition of secretion is due to the H_2 -receptor antagonism already established for other tissues *in vitro*.

There are three further, independent, pieces of evidence which establish a relationship between H_2 -receptor antagonism and the inhibition of histamine-stimulated gastric secretion. The first is negative, and defines the specificity of the inhibition of secretion. When a plateau of vagally-induced secretion was produced, in seventeen experiments, by injecting 1 IU kg^{-1} of soluble insulin intravenously, then subsequent intravenous doses of burimamide, 2×10^{-5} – $5 \times 10^{-5} \text{ mol kg}^{-1}$, produced no inhibition of secretion. Similarly, in eighteen experiments, the continuous acid secretion produced by direct, electrical stimulation of the peripheral ends of the vagi could not be inhibited. When burimamide inhibits histamine-stimulated gastric secretion, this action is not due to some unspecified suppression of the secretory process, for the stomach still responds to vagal stimulation. In these experiments, there is probably not much vagal release of gastrin from the antrum

and duodenum since the experimental technique effectively produces an acute denervation of the stomach in the region of the antral-body junction.

Evidence that the secretory inhibition is due to blockade of H_2 -receptors comes also from a comparison of the H_2 -receptor antagonist potencies of several compounds, measured *in vitro*, with their corresponding activities as inhibitors of gastric secretion, measured *in vivo*. The pA_2 values for the H_2 -receptor interaction, estimated on both atrium and uterus, were found for twelve compounds and the values varied from 3.1 to 5.2. For each compound the negative logarithm of the ED_{50} , expressed in mol kg^{-1} , was used to measure its activity as an inhibitor of histamine-stimulated gastric secretion. The atrial pA_2 -log (ED_{50}) comparison had a correlation coefficient of +0.96 and the uterine pA_2 -log (ED_{50}) correlation had a coefficient of +0.98. The H_2 -receptor antagonist activity measured *in vitro* is thus very highly correlated ($P < 0.001$) with the inhibition of histamine-stimulated gastric secretion *in vivo*.

A direct, quantitative examination of the secretory inhibition provided the third piece of evidence. The object of the experiments was to calculate the regression between the log (plasma concentration of burimamide) and log (DR-1) to provide data homologous to those obtained *in vitro*. Burimamide, labelled with tritium at the 4-position of the ring, was given by continuous intravenous infusion, at different rates, for 1 h and the plasma concentration was estimated by liquid scintillation counting after combustion; other investigations had shown that during the first hour of infusion nearly all the label was present as unmetabolized drug. Dose-ratios were measured in eighteen experiments using an assay based on a 2+1 design. Two doses of histamine were given before and then one dose was given towards the end of the infusion of burimamide. In estimating a dose-ratio, a parallel displacement of the dose-response curves was assumed. The plasma concentration of burimamide was estimated immediately before and at the peak of the test response to histamine, and an average value was used in the regression calculation. A statistically significant regression between log (DR-1) and log (B) was found. The slope of the regression, 1.07 (0.72–1.42), was not significantly different from unity and the calculated pA_2 , 5.14 (4.80–5.48), was not different from that estimated on the isolated tissues. Although the precision of this analysis is not high, the results are consistent with the proposition that burimamide inhibits histamine-stimulated gastric secretion by competitive antagonism of H_2 -receptors in the gastric mucosa.

Burimamide, which can inhibit histamine-stimulated but not vagally-stimulated secretion in the anaesthetized rat preparation, can nevertheless inhibit pentagastrin-stimulated gastric secretion. Pentagastrin ('Peptavlon', ICI) infused intravenously at $1 \times 10^{-6} \text{ g kg}^{-1} \text{ min}^{-1}$ produced a level of secretion comparable with that produced by $2.5 \times 10^{-7} \text{ mol kg}^{-1} \text{ min}^{-1}$ of intravenous histamine, and burimamide inhibited both types of secretion to a similar extent and with a similar time-course (Fig. 4). In fifteen experiments $1 \times 10^{-5} \text{ mol kg}^{-1}$ of burimamide produced $48.5 \pm 24.2\%$ inhibition of histamine-stimulated secretion and $53.2 \pm 12\%$ inhibition of a comparable level of pentagastrin-stimulated secretion in thirteen animals. The difference between these results is not significant. Pentagastrin also stimulates contractions in isolated guinea-pig ileum, which were not suppressed even by very large concentrations of burimamide, so that it is unlikely that burimamide inhibits pentagastrin-stimulated secretion by competing with pentagastrin as such for some common site. Provisionally, it seems reasonable to conclude that inhibition of pentagastrin-stimulated secretion by burimamide is related to its activity as an H_2 -receptor antagonist.

In anaesthetized cats burimamide was found to have an ED_{50} of $2.3 \times 10^{-5} \text{ mol kg}^{-1}$ for inhibition of maximal histamine-stimulated secretion and an ED_{50} of $1.6 \times 10^{-5} \text{ mol kg}^{-1}$ for inhibition of maximal pentagastrin-stimulated secretion; these values are not significantly different.

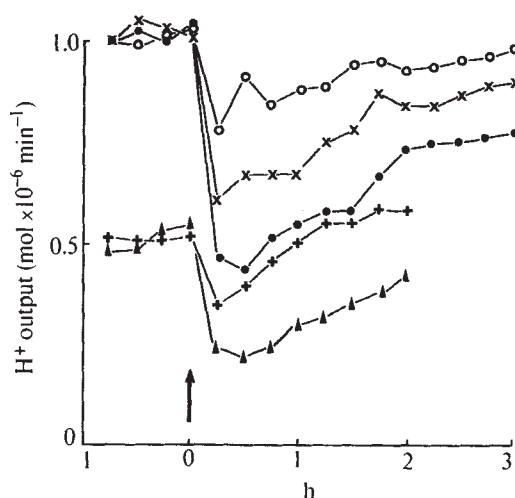


Fig. 5 Gastric acid output from dogs prepared with Heidenhain pouches. Burimamide was given intravenously at zero time (arrow). Each output curve is the mean of six experiments; the upper three curves were obtained with histamine $2 \times 10^{-5} \text{ mol h}^{-1}$ intravenously, and the lower two curves with pentagastrin $8 \times 10^{-6} \text{ g kg}^{-1} \text{ h}^{-1}$ intravenously. Doses of burimamide, mol kg^{-1} , were as follows: during histamine, ○, 1×10^{-5} ; x, 2×10^{-5} ; ●, 4×10^{-5} ; and during pentagastrin, +, 2×10^{-5} ; ▲, 4×10^{-5} .

The effects of burimamide on gastric secretion were studied on six male dogs which had been prepared with Heidenhain pouches 1–3 yr beforehand. Burimamide alone, in doses up to $4 \times 10^{-5} \text{ mol kg}^{-1}$ given intravenously, did not stimulate acid secretion in nine experiments. Preliminary experiments established that maximal histamine-stimulated secretion was produced by a continuous intravenous infusion of histamine of $2 \times 10^{-5} \text{ mol h}^{-1}$. When maximal secretion was reached, intravenous injection of burimamide at $1 \times 10^{-5} \text{ mol kg}^{-1}$ produced $28.2 \pm 6.0\%$ inhibition of secretion (Fig. 5), reaching a minimum in 15–30 min and then recovering with a half-time of about 90 min. A dose of $2 \times 10^{-5} \text{ mol kg}^{-1}$ produced an inhibition of $52.0 \pm 6.0\%$, and $4 \times 10^{-5} \text{ mol kg}^{-1}$ produced an inhibition of $75.0 \pm 7.5\%$ when tested in the six dogs. An ED_{50} for this inhibition was calculated to be $1.9 \times 10^{-5} \text{ mol kg}^{-1}$.

The inhibitory effects of burimamide on pentagastrin-stimulated secretion are also shown in Fig. 5. Pentagastrin infused intravenously at a rate of $8 \times 10^{-6} \text{ g kg}^{-1} \text{ h}^{-1}$ produced maximal secretion, although this level was about 60% of the corresponding maximum for histamine. In the six dogs, burimamide $2 \times 10^{-5} \text{ mol kg}^{-1}$ produced an inhibition of $51.7 \pm 4.9\%$, and $4 \times 10^{-5} \text{ mol kg}^{-1}$ produced an inhibition of $67.6 \pm 5.2\%$. There were no significant differences between histamine and pentagastrin in percentage inhibition and the time-course of recovery produced by burimamide.

The effects of burimamide on gastric secretion evoked by feeding have been examined in each dog. Dogs fed a large meal of tinned meat produced a level of acid output which was much less than the maximum which could be produced by histamine or carbachol but was fairly close to the level of maximum secretion produced by pentagastrin. Burimamide given in an intravenous dose of $4 \times 10^{-5} \text{ mol kg}^{-1}$ to each dog produced an inhibition of $64.4 \pm 3.2\%$ of food-stimulated secretion. This degree of inhibition is not different from that produced by the same dose of burimamide on histamine-stimulated and pentagastrin-stimulated secretion.

Finally, burimamide was given during maximal carbachol-stimulated secretion. A dose of $4 \times 10^{-5} \text{ mol kg}^{-1}$ failed to inhibit this secretion just as was found for vagally-stimulated secretion in rats.

Pharmacology trials on healthy human volunteers have been conducted by Mr J. H. Wyllie, FRCS, of the Department of

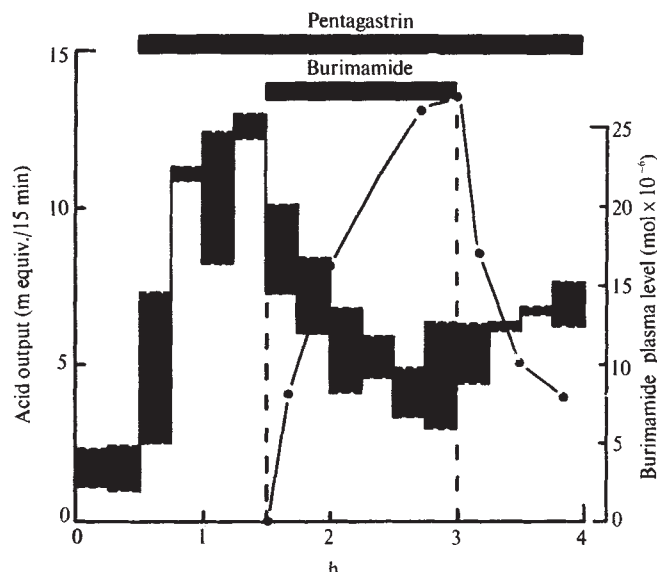


Fig. 6 Gastric acid output from human volunteers. Mean ($\pm$ s.e.) acid output from two subjects given pentagastrin 6×10^{-6} g kg $^{-1}$ h $^{-1}$ intravenously. Burimamide 3×10^{-1} g h $^{-1}$ was given intravenously along with pentagastrin for 1.5 h as shown. Plasma levels of burimamide are superimposed.

Surgery, University College Hospital Medical School. Details will be published later, but a summary is relevant for comparing the effects of burimamide on gastric secretion in different species. Gastric juice was aspirated continuously from an intragastric tube and juice was sampled and titrated at 15 min intervals. Pentagastrin infused intravenously at a rate of 6×10^{-6} g kg $^{-1}$ h $^{-1}$ had been shown to produce a maximum rate of gastric secretion in human subjects, reaching a plateau in about 1 h and maintaining it for at least 2 h 12 . When a continuous intravenous infusion of burimamide, at a rate of 3×10^{-1} g h $^{-1}$, was superimposed on pentagastrin-stimulated secretion in two subjects the total acid output was reduced by about 80% after 90 min (Fig. 6). The decline in acid output corresponded to the increase in the plasma concentration of burimamide. A similar rate of onset, and degree, of inhibition was found when burimamide 3×10^{-1} g h $^{-1}$ was infused intravenously during maximum acid secretion produced by continuous intravenous infusion of histamine at a rate of 4×10^{-5} g kg $^{-1}$ h $^{-1}$.

Essentially the same pattern of pharmacological activity—inhibition of pentagastrin-stimulated secretion as though this was a consequence of H $_2$ -receptor blockade—has thus been seen in each of the four mammalian species investigated.

Histamine Receptors in Cardiovascular System

Insofar as H $_2$ -receptor antagonism seems to be the dominant pharmacological action of burimamide, any pharmacological actions of histamine which are not easily antagonized by mepyramine should be tested for sensitivity to blockade by burimamide. The effects of large doses of histamine on blood pressure is an obvious example since these effects are known to be refractory to mepyramine 13 . The interaction between burimamide and histamine on blood pressure has been investigated in ten cats anaesthetized with chloralose. Intravenous doses of histamine between 2×10^{-8} and 2×10^{-7} mol kg $^{-1}$ produced depressor responses which could not be antagonized by mepyramine given as 1×10^{-2} g kg $^{-1}$ intravenously and repeated three or four times. These histamine depressor responses were subsequently blocked completely when burimamide was given at 3×10^{-6} mol kg $^{-1}$ min $^{-1}$ for 30 min. Histamine depressor responses at 2×10^{-9} mol kg $^{-1}$ could be partially antagonized by mepyramine; the resistant part of these depressor responses

could be antagonized completely by burimamide given at 3×10^{-7} mol kg $^{-1}$ for 30 min. Burimamide given without treatment with mepyramine was, however, more or less ineffective as an antagonist of histamine depressor responses. The cardiovascular effects of histamine are thus consistent with the involvement of both H $_1$ and H $_2$ -receptors in the response.

A related example is the difficulty in totally suppressing, by pretreatment with mepyramine, focal oedema produced by local injection of histamine 14 . Burimamide, in combination with mepyramine, is highly effective in blocking these local effects of histamine on the vascular system. There are, however, other experimental inflammatory reactions, not produced by histamine administration, which can be inhibited by burimamide; the various correlations and regressions which were used to analyse the actions of burimamide on gastric secretion obviously cannot be used to analyse these anti-inflammatory actions and it will be difficult to show whether or not they are due to H $_2$ -receptor antagonism.

Summary and Conclusions

Mepyramine has been defined as an H $_1$ -receptor antagonist 1 and burimamide has now been defined as an H $_2$ -receptor antagonist. Used alone, burimamide can antagonize those responses to histamine, such as stimulation of acid gastric secretion, which cannot be blocked by mepyramine; histamine apparently activates H $_2$ -receptors to produce these effects. Histamine responses, such as hypotension which can only be partially antagonized by mepyramine alone can be completely blocked by mepyramine and burimamide given in combination; both H $_1$ and H $_2$ -receptors seem to be activated by histamine to produce effects of this kind.

As well as blocking certain effects of histamine, burimamide inhibits pentagastrin-stimulated acid secretion, although direct cholinergic secretion seems to be unaffected. McIntosh 15 proposed that histamine in the gastric mucosa might be the local common mediator for physiological stimulation of secretion. Since then, much evidence has been presented both for 16 and against 17 the hypothesis that histamine is necessarily involved in the actions of gastrin. The evidence from burimamide is that the inhibition of pentagastrin-stimulated and food-stimulated secretion is quantitatively indistinguishable from the inhibition of histamine-stimulated secretion. This relationship must tip the balance of opinion towards the idea that the actions of gastrin are somehow coupled to those of histamine.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Solar Modulation and the Chemical Composition of the Cosmic Radiation

THE intensity variations of the cosmic radiation during the solar cycle can be well simulated by assuming a heliocentric decelerating potential that is applied to the particles arriving from interstellar space^{1,2}. During the past few years experimental and theoretical understanding of the process of solar modulation has improved greatly. It now seems that a full treatment of the diffusive-convective motions of the particles in the radially expanding solar wind results in an energy loss by the individual particles which can, on average, be treated as analogous to the effects of a potential, except for particles of quite low energies ≤ 100 MeV, where the analogy fails.

Thus in 1965 we² deduced that the previous solar cycle, from 1954 to 1965, had been characterized by a potential that ranged from 50 MV up to 700 MV and down again to 125 MV. During the present solar cycle the improved data have led to very similar estimates. Lezniak and Webber³ find 140 MV for 1965, 320 MV for 1968, and in an analysis referred to by Webber *et al.* (unpublished) 600 MV for 1970. Similarly, Goldstein *et al.*⁴ find a mean energy loss in 1965 of 210 MeV for protons, which is generally equivalent to a potential of 210 MV, at least at high energies.

The purpose of this communication is to propose a further experimental test of the validity of this model and to suggest that certain conflicting results in the literature may be reconcilable when the effects of energy loss are taken into account. The central issue is the effect of time variable energy losses on the composition of the cosmic ray nuclei. Many of the elements observed in the cosmic radiation are believed not to have had any significant abundance at the sources, but to be the consequence of fragmentation processes occurring during the propagation of heavier nuclei through interstellar matter. Thus lithium, beryllium, boron and fluorine seem to be essentially absent at the source, while Webber *et al.* have shown that none of the elements between chlorine and iron, $17 \leq Z \leq 26$, is present at the source with more than 2% of the iron abundance, apart from calcium and iron itself.

If these fragmentation production processes are energy dependent, the observed abundances of the secondary nuclei will depend on the energy at which they are produced. Thus if the modulation process results in an energy loss between the interstellar energy, where the secondary nuclei are formed, and the observation energy, the composition will depend on the degree of modulation. Clearly, if cosmic ray nuclei undergo additional energy changes in the interstellar medium, because of processes such as Fermi acceleration or convective deceleration⁵, the analysis will be more complicated.

I will neglect possible energy changes that occur during the traversal of most of the interstellar matter. Ionization losses should be unimportant except at the lowest energies but could be allowed for in a detailed calculation.

Silberberg and Tsao (unpublished work) have developed various semi-empirical relations for calculating the relevant production cross-sections and these are generally in good agreement with experimental measurements. These relations

indicate that the "light" secondary nuclei lithium, beryllium, boron and fluorine are chiefly produced in reactions that do not show an appreciable energy dependence. One would not therefore expect the abundance of these nuclei to vary significantly during the solar cycle. The "heavy" secondary nuclei, those in the range $17 \leq Z \leq 25$, on the other hand, are produced in interactions that show a strong energy dependence. Table 1 shows the ratios of the cross-sections for iron with hydrogen at 400 MeV per nucleon and at 150 MeV per nucleon to that at more than 2.3 GeV per nucleon for the various product nuclei. It can be seen that increases of up to a factor of three are present for small mass changes while there are decreases at large mass changes that are as much as twenty.

Table 1 Production Cross-section for Iron

Product nuclei	Mn	Cr	V	Ti	Sc	Ca	K	Ar	Cl
Ratio $\frac{\sigma_{400}}{\sigma_{2,300}}$	3.04	1.77	1.85	1.52	0.88	0.67	0.39	0.29	0.44
Ratio $\frac{\sigma_{150}}{\sigma_{2,300}}$	3.23	2.10	1.78	1.37	0.59	0.37	0.18	0.05	0.06
$\sigma_{2,300}$ (mb)	52	109	49	85	17	43	28	41	16

But these large decreases are for the potassium, argon and chlorine group of elements; here the situation is confused by the fact that calcium is evidently a source element. Production from calcium will therefore be a factor and, since it should be characterized by relatively large cross-sections showing the characteristic increase with decreasing energy of small mass change interactions, this will tend to cancel the effects attributable to the production from iron.

Manganese and chromium can only be produced from iron and should therefore show the largest modulation effect. Observations made at periods of low solar activity on such nuclei, having energies in the 200–500 MeV per nucleon region, should show appreciably higher abundances than those made at solar maximum. A comparison of published results^{4,6–8} suggests that this effect may be occurring. In general, however, the experimental charge resolution obtained in these various observations has been marginal and there is no convincing evidence that a modulation effect has been observed. The highest resolution observations available at present are those of Webber *et al.* and it is interesting to notice that these authors do observe energy dependent abundances of manganese and chromium, suggesting that the production cross-sections are indeed energy dependent.

It is possible to make rough quantitative estimates of the magnitude of the expected variations in abundance that might result. If one assumes no interstellar energy losses and no primordial manganese, an explicit assumption regarding the energy dependence of the cross-sections permits an estimate of the variation. Let the cross-sections decrease exponentially between 400 and 2,300 MeV per nucleon and use the values from Table 1. Then the percentage abundance changes in manganese that would be observed at 200 and 400 MeV per nucleon for various modulating potentials are those shown in Table 2. It can be seen that on this basis a variation of some 25% would be expected between solar minimum and solar

Table 2 Variations in the Observed Abundance of Manganese at 200 and 400 MeV/n

Modulating potential (MV)	Interstellar energy (MeV/n)	Cross-section (mb)	% Reduction in abundance
Observed at 400 MeV/n			
0	400	158	0
200	470	150	6
400	550	140	13
600	630	132	18
800	720	124	23
Observed at 200 MeV/n			
0	200	203	0
200	265	186	8
400	330	173	15
600	400	158	21
800	480	147	27

maximum. The detection of such a change is within the capability of the best of present detectors. Since we are now approaching a period of decreasing solar modulation, definitive results may be available within the next few years.

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Possible Identification of GX5-1

PREVIOUS attempts to identify the X-ray source GX5-1 have been unsuccessful. An optical search of the 1.2 arc min MIT error circle¹ down to 17 mag yielded no clear candidate², and in radio observations at 4.6 and 11.1 cm no point source was detected down to a limit of 0.1 and 0.005 f.u., respectively^{3,4}. Although Milne and Dickel⁵ claimed that GX5-1 might be associated with the supernova remnant Milne 56, Ilovaisky and Ryter⁶ argue that an identification with such an extended radio source is unlikely. We report here the observation of a weak point source at the X-ray position.

Table 1 Positions for GX5-1 and Nearby Objects

	RA (1950)				Declination (1950)	
	h	m	s	s		
X-ray	17	58	04	±5.3	−25° 04' 42"	±72"*
Radio	17	58	03.5	±0.3	−25° 04' 53"	±12"
Star 3†	17	58	02.91	±0.02	−25° 04' 51.9"	±0.3"
Double	17	58	03.70	±0.04	−25° 04' 39.7"	±0.5"
	17	58	03.80	±0.04	−25° 04' 44.7"	±0.5"

* 90% confidence limits. All other quoted uncertainties are r.m.s. errors.

† From a plate taken by J. Tinbergen with the Rockefeller refractor of the Leiden Southern Station.

On July 2 and September 24, 1971, the Westerbork synthesis radio telescope operating at a frequency of 1,415 MHz (21.2 cm wavelength) was used to observe the GX5-1 region. On both occasions an unresolved source of flux density 0.010 ± 0.003 f.u. was detected close to the MIT X-ray location. Radio and X-ray positions are given in Table 1. Also included are the positions we have measured for the nearest optical objects—the 12 mag star No. 3 listed by Kunkel *et al.*², and a much fainter double star located between stars 3 and 4. The double star is not visible in Fig. 1 of the paper by Kunkel *et al.*, but is present on the deeper Palomar Sky Survey prints. On the blue print there may be a faint trace of nebulosity connecting star 3 to the double, but we cannot decide whether it is real. Judging from its position in the two-colour diagram of ref. 2, star 3 is an early B-type object at a distance of about 2.4 kpc. Thus an identification with this star would place GX5-1 in the Sagittarius spiral arm.

A positive identification of our radio source with GX5-1 must await the detection of radio variability. But the fact that other X-ray sources of comparable strength are detectable radio emitters is evidence in favour of the identification. Further optical work is also needed. In particular it would be interesting to determine whether star 3 is a binary with a large mass function as is the case for Cygnus X-1.

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Deep Sea Carbonates: Dissolution Facies and Age-Depth Constancy

DEEP sea drilling¹ has shown the presence in many parts of the seafloor of a complex sequence of carbonate sediments showing various degrees of dissolution. On the present seafloor, dissolution of carbonate increases with depth, leading to increasingly poorly preserved carbonate assemblages with increasing depth of deposition, until finally all carbonate is dissolved, leaving a residue of pelagic clay. This relationship between depth and dissolution has been used to interpret the carbonate profiles in drill sites in two contrasting ways. First, assuming that the present distribution of dissolution with depth was constant through time, poorly preserved carbonate skeletons and pelagic clay indicate great depth of deposition, whereas well preserved skeletons and pure chalk indicate a shallow ocean bottom²; second, neglecting tectonic movements, as well as redeposition, the distribution of age versus ocean depth of foraminifera, nannofossils and clay defines the rise and fall of solution levels^{3,4}, such as the calcite compensation depth (CCD) and the (whole test) foraminiferal compensation depth (FCD) somewhat above the CCD.

In view of the difference of carbonate bathymetry between various parts of the ocean^{5,6}, and the relationship of these patterns to oceanic circulation⁷⁻¹¹, the assumption of a stable dissolution versus depth curve, as in ref. 2, is unrealistic. Oceanic circulation must have responded to changing climate and geography during geological history, and the vertical distribution of carbonate facies must have varied accordingly within the different ocean basins. Postulating changes in solution levels, as in ref. 3, is therefore more reasonable. Emphasis must be given, however, to shallow occurrences of the facies showing most dissolution at any one time, to account for redeposition of carbonate into deeper water, and bathymetric control from plate tectonics must be introduced before a satisfactory picture can emerge.

Here I use the results of Sclater, Anderson and Bell¹² to extrapolate a stable age-depth relationship on spreading ridge flanks through time. Following an earlier study of Menard¹³, Sclater *et al.* made a detailed investigation of ridge flank bathymetry. They found a striking similarity for the correlation between seafloor age and depth difference of seafloor basement to ridge crest in widely separated oceanic areas. They conclude that the fit of age versus depth of basement on the present seafloor is good enough to date a given piece of low relief, spreading seafloor to within 2 m.y., from a knowledge of bathymetry alone, for ocean floor younger than 40 m.y. Ridge crest elevations are virtually constant and seem rather independent of spreading rates. This geographical constancy permits establishing a general age-depth relationship by adding depth differences (seafloor to ridge crest) to the average ridge crest elevation of 2,700 m (Fig. 1). From here on therefore age is directly compared with bathymetric depth.

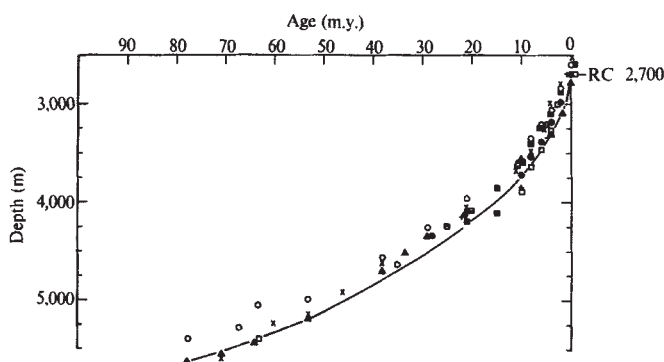


Fig. 1 Age-depth plot for the present seafloor, data from ref. 12. Fit by eye. RC, Ridge crest; Δ , North Pacific; $\circ$, South Pacific < 3 cm/yr; $\bullet$, South Pacific > 3 cm/yr; $\square$, South-east Indian; $\blacksquare$, Central Indian; $\square$, Carlsberg; $+$, North Atlantic < 40° N; $\times$, South Atlantic.

In assembling their data (from which Fig. 1 is derived), Sclater *et al.* used ocean floor without sediment cover. This introduces a certain bias in favour of elevated seafloor in areas where a sediment cover is normally present. I have consequently given weight to their (deeper-than-average) North Pacific controls to draw a "best fit" by eye. The fit suggests that actively spreading seafloor subsides 1,000 m during the first 10 m.y. of its existence, and a further 1,000 m during the following 26 m.y. Extrapolation on the basis of drilling results (Fig. 2) suggests that within 100 m.y. there is a subsidence of 3,000 m. This compares well with several estimates of Menard¹³. The points plotted in Fig. 2 were not adjusted for isostatic loading of the plate by the sediment accumulating on top of it. Such a correction would lead to somewhat shallower basement depths. The correction was omitted in view of the fact that most drill sites are biased toward shallow depths, being positioned on hills. The great similarity between Pacific, Atlantic and Indian Ocean age-depth relationships (Fig. 1) suggests a fundamental principle underlying the phenomenon¹⁴ and makes it probable that the relationship

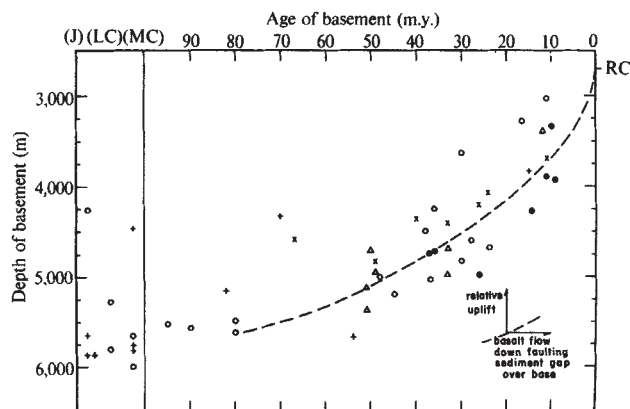


Fig. 2 Age-depth plot for the present seafloor, data from ref. 1 and refs. 20 and 21. The curve is that in Fig. 1. Some of the possible factors contributing to the scatter are indicated in the lower right hand corner. "Age of basement": age of fossils overlying basalt in which hole terminated. J, Jurassic; LC, Lower Cretaceous; MC, Mid-Cretaceous. $\bullet$, East Equatorial Pacific; $\circ$, Central Pacific; Δ , North Pacific; $\times$, South Atlantic; $+$, North Atlantic.

was valid through Tertiary time and possibly earlier. The scatter in the drilling data (selected to exclude areas not clearly related to spreading centres) cautions against neglecting local complications (Fig. 2).

The hypothesis of age-depth constancy—postulating that at any point in geological time the age of the seafloor determines how far it moved downward from the original ridge crest—provides a simple means of reconstructing the approximate depth of deposition of ancient sediments, independent of spreading rates of the underlying basement. Depths found by back-tracking sites using this hypothesis are called B-depths to distinguish them from actually measured depths.

Tracks of the basement created x years ago are plotted parallel to the present idealized age-depth curve, starting at age x and 2,700 m depth (Fig. 3). The present depths (age=0) of these tracks correspond to Fig. 1. A sample recovered from the deep sea, through coring or drilling, is plotted as follows.

First, find the age of the basement, preferably the magnetic age, since fossil ages on sediments overlying "basement" appear rather uncertain (see Fig. 2); this age defines the track

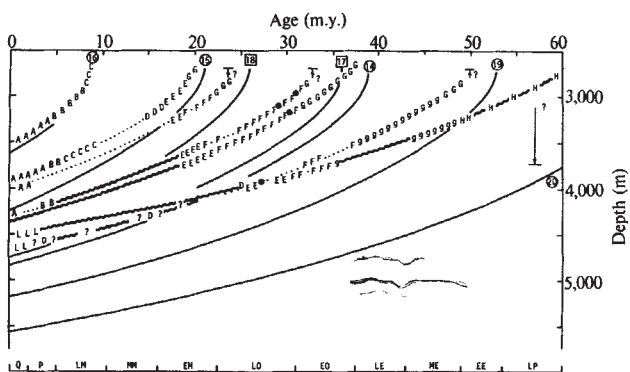


Fig. 3 Formations at 30° S, Mid-Atlantic Ridge, plotted at approximate depths of deposition (B-depths), found by back-tracking parallel to subsidence lines expected from age-depth constancy (A-depths, solid lines). A, Albatross ooze; B, Blake ooze; C, Challenger ooze; D, Discovery clay; E, Endeavor ooze; F, Fram ooze; G, Gazelle ooze; H, Grampus ooze; I, Hirondelee ooze; L, local clay units. Solid circles: Braarud-sphaera chalk. Age scale from Berggren¹⁶. Q, Quaternary; P, Pliocene; LM, Late Miocene; EO, Early Oligocene; ME, Middle Eocene; LP, Late Palaeocene. $\sim$, Hiatus; $\dots$, drilled interval. Arrows, sites 17 and 18: possibly necessary correction of depths due to faulty magnetic age; site 20: possible tectonic correction necessary. Site numbers encircled: west of ridge. Site numbers within squares: east of ridge.

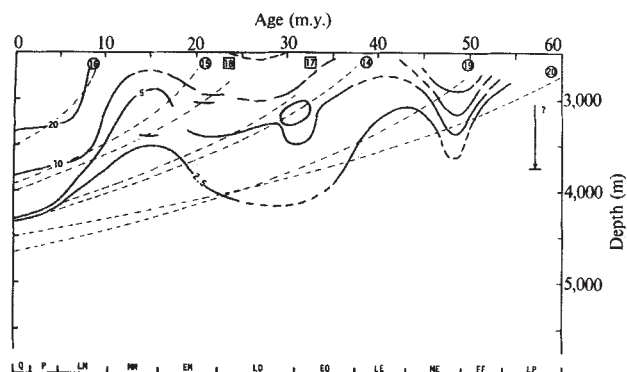


Fig. 4 Sedimentation rates in m/million years, obtained graphically, using the age scale of Berggren¹⁶. Broken lines indicate the most probable tracks of sites of deposition (B-depths), according to the hypothesis of age-depth constancy.

to be followed. Second, the expected depth of basement for this age (A-depth) will usually differ from the real one, because of original difference on the ridge crest, uplift or downwarp during subsidence along the flank, and/or loading of the crust by sediment. The isostatic effect of loading is most easily accommodated by halving all sample depths below seafloor when adding core depths to preliminary site B-depths. If the difference between actual depth and A-depth was originally present at the ridge crest, the site is moved backward through time parallel to the appropriate age-depth track, the difference between actual depth and A-depth being held constant. In fact, the place and time of any relief change are usually unknown or, at best, a matter of conjecture, so that it is as well to assume initially that depth differences of actual to ideal basement were already present near the ridge crest. Third, the most probable locations, derived by back-tracking sites and descending one-half drill depths, are marked accordingly. These locations are the final B-depths.

The carbonate facies of a profile across the Mid-Atlantic Ridge at 30° S has been described in ref. 2. A summary of this information, as well as interpretations based on CCD constancy, have been presented by Maxwell *et al.*¹⁵. The JOIDES Leg 3 data seem to be well suited to illustrate the method of back-tracking and to assess its reliability (Table 1). Results for sites 14 to 20 are presented in a dynamic age-depth diagram, the hypothetical A-depth basement tracks being shown as solid lines, labelled with the hole numbers (Fig. 3). The B-depth tracks of depositional sites are given by the strings of formation symbols A to H ("Albatross"–"Hirondelle"). According to Hsü and Andrews² differences between these formations are largely due to various degrees of dissolution. When they dissolve, deep-sea carbonates first lose the delicate species, then resistant ones, and finally all calcite, leaving an insoluble residue. Foraminifera are dissolved before the most

Table 1 Site Information

Site	Water depth m	Depth of "base-ment"	Expected depth* of base-ment	Prob-able age†	Topography
14	4,343	4,450	4,850	39	Small hill (west)
15	3,927	4,068	4,270	21	Small hill (west)
16	3,527	3,702	3,710	9	Small hill on flank of uplift (west)
17	~4,300	4,400(?)	4,750	36	Three holes: flank of hill and small basin (east)
18	4,018	4,196	4,440	26	Flat area (east)
19	4,677	4,817	5,180	53	Flank of a ridge (west)
20	4,512	~4,580	5,530	71	Slope of a ridge (west)

* From Fig. 1, corrected for isostasy (A-depth).

† Based on magnetic lineations.

resistant nannofossils. As the insoluble terrigenous components are concentrated, colours change from white to brown.

Using these clues, Hsü and Andrews² assigned the following labels to the formations: "alytic" (not dissolved), "eolytic" (signs of initial dissolution), "oligolytic" (slightly dissolved), "mesolytic" (moderately dissolved) and "hololytic" (completely dissolved). Additional (and more reliable) information regarding differences between the various formations is given by carbonate percentages and by sedimentation rates (Table 2, Fig. 4).

Assuming that maximum sedimentation rates represent undissolved facies, missing percentages can be estimated and, since losses increase with depth, they may be largely ascribed to solution. The dissolution estimates (Table 2) compare well with the assessments of Hsü and Andrews in that they correspond to the solution sequence derived by these authors. The nomenclature they used, however, appears misleading. Deposition rates for non-carbonate sediment vary from 1 m to 3 m.y.; the 2.5 isoline (Fig. 4) is therefore at or somewhat above the CCD, back to about 35 m.y. ago. For sediments older than 40 m.y., the situation seems more complicated.

Reconstruction of deposition patterns by age-depth constancy (Figs. 3, 4) allows the following observations. At any one time, less dissolved facies overlie more dissolved ones, since dissolution increases with depth. (To what extent dissolution during settling contributes to this effect is not known.) There is one apparent exception, involving a discrepancy of some 400 m (E-marl over F-ooze at 19 m.y.). This solution differential may be an effect of Antarctic Bottom Water (AABW), which flows northward west of the ridge, dissolving carbonate (site 15), but is barred from the eastern flank by the Walvis Ridge (site 18)¹⁷. If true, the existence of an east-west dissolution differential for the past 20 m.y. and its negligible influence in the Oligocene (compare sites 14 and 17) suggest an important change in bottom water

Table 2 Characterization of Carbonate Formations

Formation	Foraminifera (ref. 15) (approx. %)	Terrigenous components (ref. 15) (approx. %)	Solution* facies	CaCO ₃ † (%)	Sedimentation‡ rates (m/m.y.)	Carbonate dissolved§ (%)	
						Range	Average
Albatross	> 10	< 10	Eolytic	77–91	5–20	0–73	36
Blake	< 10	< 10	Oligolytic	88–91	5–20	31–76	61
Challenger	< 10	10–20	Oligolytic	80–90	10	44–70	57
Discovery	0	55–100	Chiefly hololytic	0–50	1–4	91–100	96
Endeavor	1–8	20–60	Mesolytic	37–80	4–10	86–96	91
Fram	1–3	20–30	Oligolytic	73–85	5–20	0–82	56
Gazelle	< 3	40–60	Mesolytic	34–68	1–10	87–96	92
Grampus	< 10–15	20–30	Chiefly oligolytic	79–84	5–20	0–80 (?)	44 (?)
Hirondelle	10	~ 30	Chiefly mesolytic	74	1–2	96	96

* Ref. 1, 3, 453. † Ref. 1, 3, 449.

‡ Obtained graphically from bio-ages and Berggren's¹⁶ time scale using data in ref. 1, 3.

§ Assuming that all variation in carbonate sedimentation rate is due to solution and maximum rate (A, site 16; F, site 18; G, site 18) is undissolved chalk. Data from ref. 1, 3, 451.

circulation at the beginning of the Miocene. The discrepancy in sedimentation rate profile of site 18 shows the same pattern in greater detail. An east-west fertility gradient may also play a role. Unfortunately, the crucial interval allowing investigation of the east-west differential was drilled, not cored.

Non-deposition and erosion, especially well documented for the Miocene record, are the more pronounced the greater the depth of deposition. This is expected if dissolution and the active flow of bottom water increase with depth and if these agents are responsible for the nonconformities observed. The eastern site 17 and the western site 14 show similar patterns, suggesting that non-deposition at 3,750 m depth started a little after 20 m.y. ago in both basins, unless, by chance, backward erosion proceeded to isochronous levels at these sites. Intense solution at depths below 4,000 m in both basins appears a likely agent for preventing accumulation of calcareous sediments during most of the Miocene. An east-west solution differential again seems to be present: the hiatus at 17 may be less complete than that of 14. Unfortunately, the interval was not bracketed by coring. In the western basin, and at greater depths (sites 19, 20), non-deposition started earlier, unless considerable backward erosion took place. Since nonconformities are bounded by slowly accumulating facies, however, deposition probably ceased gradually. Non-deposition and intermittent erosion at 4,000 m depth in the western trough consequently started 25 m.y. ago.

The trend of increased dissolution during Middle Miocene, terminated by enhanced calcareous sedimentation during the Pliocene, agrees with the trend in the North Atlantic (sites 10, 12, *JOIDES* 2 (ref. 1), and site 140, Scientific Staff, Leg 14 (ref. 18); see also Hay^{3,4}). Ocean-wide trends within the Atlantic are expected, if bottom water circulation (influx of AABW, onset of North Atlantic Deep Water production) and exchange with the Mediterranean (possible closing and reopening of Straits of Gibraltar¹⁹) and the Pacific (closure of Panama Isthmus) are responsible for the changes in carbonate patterns through time. Local tectonic uplift and subsidence would not provide this agreement over a large area.

Major redeposition of ridge chalk downward may have played a part in forming *Braarudosphaera* chalks at site 14, since sedimentation rates here are unusually high.

The lack of control for pre-Oligocene patterns and the possible complexity of the pre-Oligocene bathymetry of site 20 (which is much too shallow for its age) make interpretation of this part of the record rather hazardous. Among other factors, the relative importance of mechanical erosion and non-deposition and of chemical dissolution in Gazelle and Hirondelle Formations must be clarified before low sedimentation rates within these units can be explained. (Being part of the Rio Grande Rise, the local tectonic history of sites 21 and 22 may be even more complicated. For the purpose of establishing general patterns, I have disregarded them.) The one available site from the North Atlantic that is instructive for comparison of pre-Oligocene carbonate history is site 10 of *JOIDES*, Leg 2. At this site, sediments apparently were laid down near the CCD throughout Early and Middle Eocene. According to age-depth constancy, the site moved down-flank during this time by some 250 m. The CCD may have moved downward by the same distance.

It appears that the present distribution of carbonate facies is largely a result of seafloor spreading, changes in dissolution levels, and local tectonism and redeposition processes. The hypothesis of age-depth constancy is well founded in present day observation and allows mapping of the major features of the carbonate record, at least for the post-Eocene in the Atlantic Ocean. (E. L. Winterer used the age-depth data of Sclater *et al.*, as well as other variables, to account for the distribution of sediment thicknesses in the equatorial Pacific: annual meeting of Geol. Soc. America, Washington, DC, November 1971.) Once bathymetrically controlled ancient dissolution levels have been reconstructed for the ridge flanks for various geological times, it will be possible to use these levels

to follow the history of oceanic circulation as well as to elucidate tectonic movements in more complicated regions.

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Chlorinated Hydrocarbon Residues in Airborne Fallout

IN an analysis of the input and output of chlorinated hydrocarbon residues in a freshwater ecosystem in south Sweden, the amount entering the study area by means of precipitation and by airborne particles was estimated.

The fallout was trapped on a 200 µm nylon net (30 × 30 cm) which, in a standardized procedure, had been impregnated with a thin film of silicone oil (SE 30). The chlorinated hydrocarbons are collected and retained in the oil. Small particles, organic as well as inorganic, also become firmly attached to the net.

The impregnated nets were exposed in open places for 2-3 months. After collection, the nets were washed in Soxhlet extractors with n-hexane for 2 × 24 h. The hexane solution was evaporated to a suitable volume, cleaned by treatment with concentrated sulphuric acid and dried with anhydrous sodium sulphate and silica gel. An aliquot of the extract was injected on a gas chromatograph with electron capture detectors, and the relative retention times were estimated and compared with retention times of known substances. As a reference for polychlorinated biphenyls (PCB), a commercial product ('Clophen A 50') was used.

The samples were run on three different columns with SF 96 (4%), QF 1 (8%) and SF 96/QF 1 (3 : 1) as the stationary phases on 'GasChrom P' (100/120 mesh). The temperatures of the injection block, column and detector were 225°, 175° and 190° C, respectively.

The identity of the more important peaks in the chromatograms was confirmed by chemical methods. *p,p'*-DDT was hydrolysed to *p,p'*-DDE by boiling with alkali solutions, and

this product was estimated by gas chromatography. *p,p'*-DDE, which interfered with some of the PCB peaks, was decomposed by oxidation with chromic acid. The chemical procedures did not affect the polychlorinated biphenyls¹.

The relative frequency of wind directions in the area of the fallout stations during the year (average values from 1961–1965) shows that the most frequent direction is W to SW (Fig. 1). This means that the study area is subjected to airborne material originating from industries along the Swedish west coast and in the Copenhagen area, as well as from heavily industrialized districts in West Germany. Stations A, D, E, F and G are situated in agricultural districts, station C in the city of Lund and station B in the city of Malmö, close to a disposal plant for municipal refuse.

The average monthly levels in ng/m^2 of ΣDDT (*p,p'*-DDT + *p,p'*-DDE) and PCB trapped in the fallout devices during 3 months (January, February and March 1971) show significant differences in the regional distribution of chlorinated hydrocarbon residues in the airborne fallout (Fig. 1). High levels of PCB were recorded in the western part of the region; for ΣDDT , no such distinct distributional pattern was found. In some of the samples analysed, unidentified electron-absorb-

ing substances were also found; these are being subjected to mass-spectrometric investigations.

The differences between stations A and B are small, in spite of their different locations. Station A, situated on the seashore in an agricultural district, shows higher levels of PCB than station B, located just outside a big disposal plant for municipal refuse. At this plant, daily incineration of garbage is usual and it might be expected that waste products containing PCB would be burnt with the varied refuse. Being highly resistant to heat, polychlorinated biphenyls escape to the atmosphere and contaminate the environment. Since the wind direction is most frequently W to SW, station A is subjected chiefly to airborne products originating from across the Sound (Öresund), while station B (located east of the disposal plant) is also exposed to fallout from the plant.

A local source is presumably responsible for the relatively high amount of PCB recorded at station D, although the origin of this deposit is still unknown.

Stations C, E, F and G showed small to moderate levels of PCB, as was the case with station H, located in a forest district in south-central Sweden (Table 1). The amount of PCB and ΣDDT collected at station E from August 1969 to December

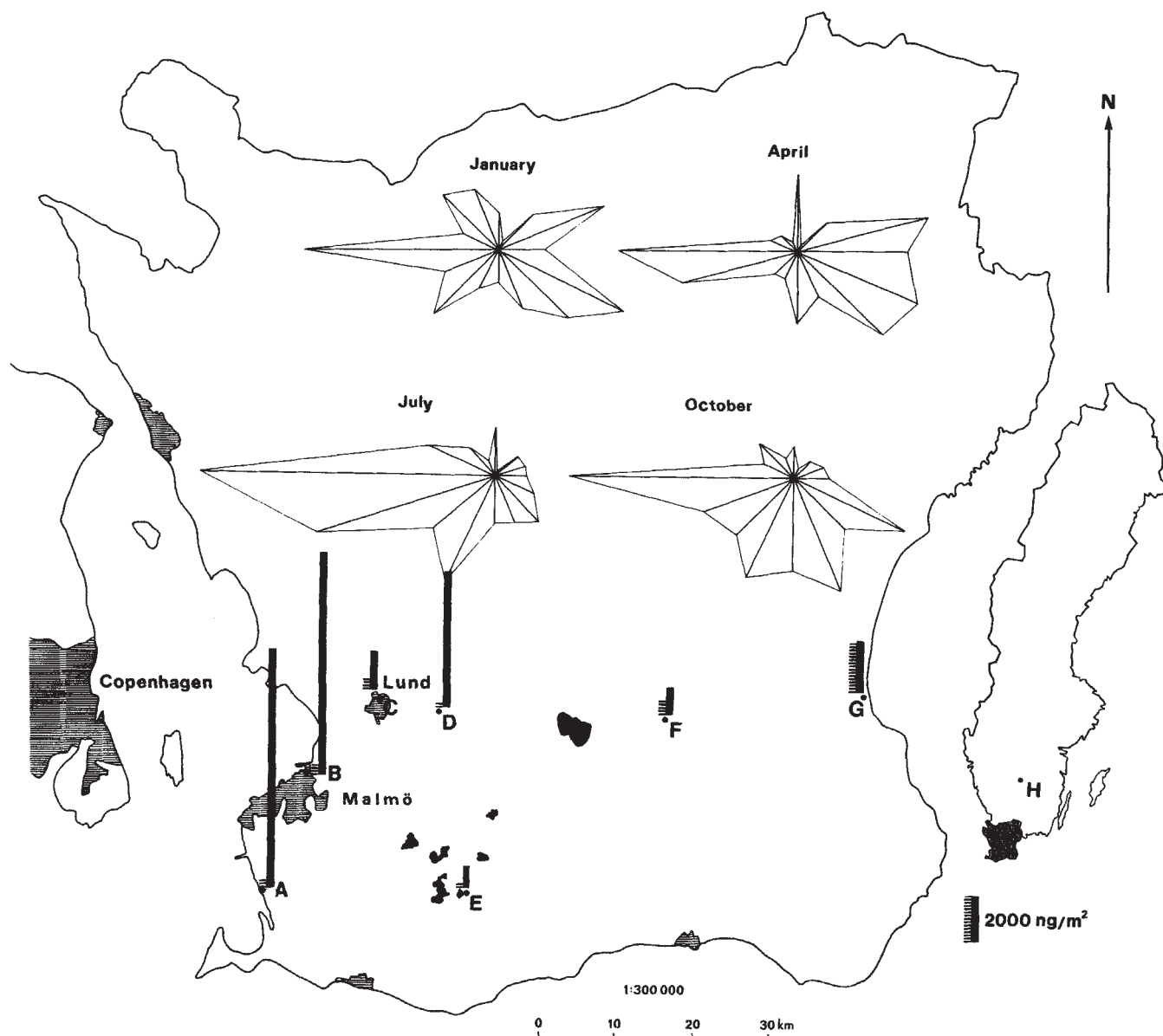


Fig. 1 Average monthly levels of PCB and ΣDDT in airborne fallout collected in south Sweden ($\text{ng m}^{-2} \text{ month}^{-1}$). Relative frequency of wind directions is indicated in the upper part of the figure.

1970 was fairly constant, but there was a significant increase in PCB collected during the period February to April 1970. Compared with the rest of the year, this period was characterized by a high mean precipitation (78 mm/month) which probably influenced the amount of airborne particles deposited.

Table 1 Average Monthly Levels of Σ DDT and PCB in Airborne Fallout collected in South Sweden ($\text{ng m}^{-2} \text{ month}^{-1}$). The Symbols for the Collection Sites refer to Fig. 1. Σ DDT = p,p' -DDT + p,p' -DDE

Collecting site	Period of collection	Σ DDT	PCB
A	January–March 1971	330	10,510
B	January–March 1971	415	9,860
C	January–March 1971	460	1,740
D	January–March 1971	170	5,980
E	August–October 1969	1,200	910
	February–April 1970	1,350	4,460
	May–July 1970	1,300	1,590
	August–October 1970	690	550
	November–December 1970	230	1,800
	January–March 1971	200	850
F	January–March 1971	1,650	1,900
G	January–March 1971	2,075	2,190
H	January–March 1971	100	620

The regional distribution of Σ DDT was more uniform than that of PCB. In the study area, DDT has been used in moderate quantities mainly for spraying various crops. Since 1970, the use of DDT in gardening and agriculture has been prohibited in Sweden and only a restricted amount is being used in forestry. In spite of these restrictions, DDT was found in airborne material collected at various stations. It is not clear whether the DDT originated within the region or had been transported from places far away.

It has been shown that nearly half the amount of DDT applied to the surface of the soil in field conditions may volatilize, thus making a slow, long term contribution to the atmosphere². Direct drift has been found to occur from spraying operations, especially when using aerial application³.

The origin and general routes of transport of PCB compounds to the environment are, however, not fully understood. They are not spread around on the land as pesticides, but are used chiefly in industry as heat transfer media, lubricants and for insulation. They are also used in paints, varnishes, waxes and synthetic resins to improve chemical resistance, adhesiveness and flexibility^{4,5}. Vapours and effluents from industrial processes using PCB compounds may contribute to their dispersal as may discarded manufactured products. Holden⁶ has shown that crude sewage sludge can constitute a source of entry to the environment.

In a study of chlorinated hydrocarbon residues in rainwater, Abbott⁷ demonstrated that the higher levels of DDT found in London rainwater, compared with that from a rural area, could be attributed to London air having a higher content of particulate matter, for which DDT has affinity. There is no estimate of the distribution of particulate matter in the air of the study area, but it is assumed that the atmosphere in the more populated and industrialized parts (for example, the region along the Sound) is more polluted than elsewhere. Because PCB also has strong affinity for particulate matter, the same mechanism of dispersal in the atmosphere may operate for both substances, thus influencing the regional distribution of PCB.

The evidence presented here indicates a general occurrence of PCB compounds in airborne fallout. It is suggested that transport by air or airborne particles is one of the main routes in the dispersal of PCB. In southern Sweden, there is regional variation in PCB levels. Correlated with the prevailing winds it is suggested that part of the PCB compounds originated not within the study area but further afield.

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Plasma Pyrolysis of Coal

WHEN coal is heated rapidly to temperatures above 1,250° C, the emitted volatiles are cracked to yield lower hydrocarbons which, if conditions are favourable, will consist mainly of acetylene. Such conditions involve reaction times of only a few milliseconds coupled with very rapid quenching rates.

A variety of energy sources has been used to achieve rapid heating rates^{1–7}. Although the temperatures and residence times to which the coal has been subjected in these various investigations differ widely, there is a similarity in the nature of the products obtained. The products consist principally of soot and gas; in most cases little or no tar is formed. At the temperatures used acetylene formation is thermodynamically favoured and significant quantities can be detected in the gas.

Work on the high temperature pyrolysis of coal started at Sheffield in 1962. James⁸, and later Deyasi⁹, pyrolysed coal

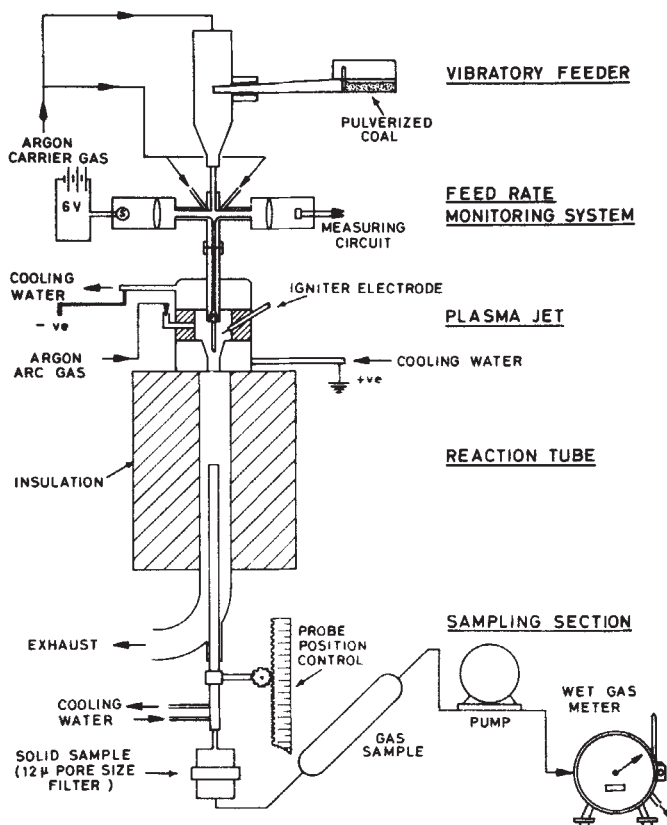


Fig. 1 Schematic diagram of plasma jet apparatus.

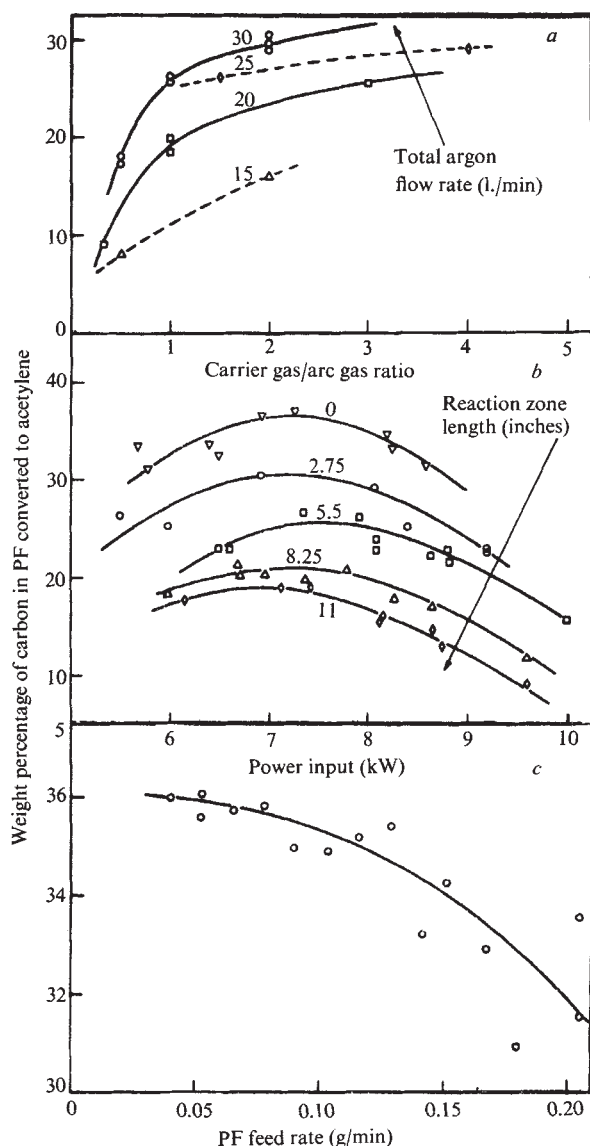


Fig. 2 Effect of operating conditions on yield of acetylene—Barnborough coal. *a*, PF feed rate, ~ 0.1 g/min; power input, 7 kW; reaction zone length, 2.75 inches. *b*, PF feed rate, 0.1 g/min; arc gas flow rate, 10 l./min; carrier gas flow rate, 20 l./min. *c*, Power input, 7 kW; reaction zone length, zero; arc gas flow rate, 10 l./min; carrier gas flow rate, 20 l./min.

in an arc-image furnace. It was found that a yield of volatiles in excess of that indicated by the BS volatile matter test¹⁰ was obtained and 8.2% by weight of carbon in the coal was converted to acetylene. These results led James¹¹ to use an argon plasma jet as the heat source in an attempt to improve the acetylene yield by increasing the heating rates and shortening the residence times. Complete devolatilization of the coal was not achieved, the amount of volatile matter remaining being equivalent to 20 to 70% of the original volatile matter content. James concluded that the penetration of the coal-carrier gas stream, which was injected radially into the plasma stream, was a critical factor in the devolatilization of coal. In spite of the poor mixing, a maximum of 24% of carbon appeared as acetylene.

The objectives of this latest investigation were, first, to improve the efficiency of pyrolysis with respect to acetylene formation and, second, to obtain further knowledge of the pyrolysis mechanism^{12,13}.

To ensure that the coal was introduced into the hottest region of the plasma, it was fed axially into the plasma through holes drilled in a hollow cathode holder. A schematic diagram

of the apparatus is shown in Fig. 1. The principal argon arc gas stream was introduced tangentially into the plasma jet and the pyrolysis products passed through a reaction tube to the quenching and sampling systems. Power for the plasma jet was supplied by a 22 kW d.c. generator.

The four coals shown in Table 1 were subjected to pyrolysis in identical conditions. The gaseous pyrolysis products (see Table 2) consisted mainly of hydrogen, acetylene and carbon monoxide. No carbon dioxide was detected, but hydrogen cyanide was present in trace quantities. The carbon monoxide content corresponded closely to the maximum theoretical yield based on the oxygen content of the coal. A typical inert-free product composition consisted of hydrogen 46, acetylene 31 and carbon monoxide 23% by volume.

As Fig. 2 shows, the yield of acetylene was governed by the operating conditions. Maximum yields were obtained at the shortest residence times and lowest feed rates employed and at an optimum power input of about 7 kW. With longer residence times and greater power inputs the cracking of acetylene to its elements occurred to a much greater extent. With the exception of runs carried out at the lowest power inputs, the amount of hydrogen appearing as molecular hydrogen or hydrocarbons approximated to the hydrogen content of the coal.

Examination of the solid products of pyrolysis indicated that drastic size reduction had taken place and that a considerable quantity of fine soot had been formed. The particle degradation was attributed to the extremely high heating rates that were used.

Fig. 3 shows that the yield of acetylene obtained from the Barnborough coal of volatile matter content 36.02% by weight (d.a.f.) was equivalent to a conversion of 36.6% by weight of carbon in the coal to acetylene. For the perhydrous Peckfield coal of volatile matter content 47.8% by weight (d.a.f.) the corresponding conversion to acetylene was 46%. When the carbon monoxide contents were taken into account the yield of volatiles was up to 25% greater than the BS volatile matter content.

It is considered that acetylene is formed principally from the aliphatic and alicyclic components of the coal structure. Generally, for coals, the proportion of non-aromatic material is related to their volatile matter contents. This hypothesis is supported by results from complementary experiments using

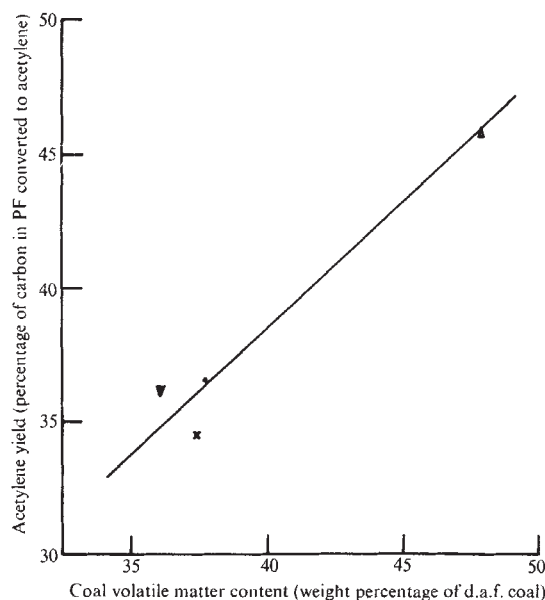


Fig. 3 Acetylene yields as function of coal volatile matter. Power input, 7 kW; arc gas flow rate, 10 l./min; carrier gas flow rate, 20 l./min; reaction zone length, zero; PF feed rate ~ 0.1 g/min. ●, Sample No. 1; ▼, sample No. 2; ×, sample No. 3; △, sample No. 4.

coal tar pitch and methane as feedstocks. The maximum yield of acetylene from pitch was only 34.5% on a carbon basis, chiefly because of its highly condensed aromatic structure, whereas the yield from methane was 87.9%.

The cracking of aliphatic and alicyclic fragments approximating to the general formula C_nH_{2n} to form acetylene as the ultimate product involves dehydrogenation steps resulting in the appearance of at least one molecule of hydrogen for each molecule of acetylene formed. This imposes an upper limit on the yield of acetylene from a given coal. The maximum yields obtained from the four coals investigated are all very close to

their limiting values. A typical limiting curve for the Barnborough coal is shown in Fig. 4.

Possible means of increasing the limiting values are by adding more hydrogen to the coal structure by hydrogenation before pyrolysis or by pyrolysing the coal in the presence of a significant partial pressure of hydrogen.

In an attempt to improve the acetylene yields, argon/hydrogen mixtures were used as the principal arc-gas. The maximum concentration of hydrogen at which the arc was stable was 10% by volume. Nevertheless, Table 3 shows that significantly improved yields of acetylene were obtained. A maximum

Table 1 Analytical Data of Coal and Pitch Samples

a, Coal samples

Sample No.	Colliery and seam	NCB code No.	Proximate analysis, % by weight (air dried basis)			Ultimate analysis, % by weight (d.a.f. basis)					VM present by weight (d.a.f. basis)	Carbon/hydrogen ratio by weight
			H ₂ O	Ash	VM	C	H	N	S	O*		
1	Calverton, High Main	902	5.29	6.61	33.20	79.80	5.01	1.90	0.79	12.50	37.68	15.94
2	Barnborough Main, Newhill	702	2.81	4.43	33.41	80.35	5.34	1.92	1.88	10.51	36.02	15.05
3	Ferry Moor, Shafton	802	3.35	7.00	33.51	83.97	6.23	1.97	2.44	5.39	37.38	13.45
4	Peckfield, Beeston	Perhydrous	0.85	2.95	45.98	83.58	6.44	1.61	1.54	6.83	47.80	12.96

b, Pitch sample

Source	Sample	Ultimate analysis, % by weight (as received basis)						Ring and ball temp. °C	Mean molecular weight	Carbon/hydrogen ratio by weight
		C	H	N	S	Ash	O*			
Rexco Research and Development Co. Ltd	R.1396	83.52	7.42	1.45	0.95	0.17	6.49	74.	342	11.26

* By difference.

Table 2 Gaseous Products of Pyrolysis (Coal Sample No. 2 of Table 1)

Run No.	Power input (kW)	PF feed rate (g/min)	Argon flow rates (l./min)		Gas analysis, % by volume						C ₂ H ₂ yield (% by weight of C in dry coal)	CO yield (% by weight of C in dry coal)	H ₂ in gaseous products (% by weight of H in dry coal)
			Arc	Carrier	H ₂	CO	C ₂ H ₂	C ₂ H ₄	C ₂ H ₆	CH ₄			
1	7.20	0.080	5	10	0.259	0.085	0.0612	0.0003	Nil *	0.0006	16.03	11.13	105.70
2	6.80	0.100	10	5	0.332	0.102	0.0380	0.0002	Nil	0.0005	7.96	10.69	97.62
3	7.00	0.110	5	15	0.190	0.080	0.1010	0.0003	Nil	0.0007	25.66	10.16	93.16
4	6.84	0.070	10	10	0.137	0.050	0.0500	0.0003	Nil	0.0006	19.96	9.98	94.64
5	7.20	0.075	10	10	0.179	0.060	0.0495	0.0002	Nil	0.0006	18.44	11.18	107.55
6	7.20	0.090	15	5	0.225	0.065	0.0285	0.0002	Nil	0.0004	8.85	10.09	99.20
7	7.00	0.097	5	20	0.122	0.052	0.0802	0.0003	Nil	0.0004	28.88	9.36	91.72
8	6.83	0.100	10	15	0.149	0.060	0.0751	0.0002	Nil	0.0005	26.23	10.48	98.60
9	6.93	0.110	10	20	0.113	0.054	0.0797	0.0003	Nil	0.0006	30.37	10.29	92.95
10	6.90	0.097	10	20	0.102	0.050	0.0682	0.0003	Nil	0.0006	29.47	10.80	93.19
11	7.37	0.097	10	20	0.120	0.051	0.0671	0.0003	Nil	0.0006	28.99	11.02	102.11
12	6.85	0.095	15	15	0.103	0.046	0.0595	0.0002	Nil	0.0004	26.25	10.15	90.62
13	6.84	0.090	15	15	0.125	0.047	0.0548	0.0002	Nil	0.0003	25.52	10.94	105.76
14	6.84	0.095	20	10	0.133	0.047	0.0407	0.0001	Nil	0.0004	17.96	10.37	96.50
15	7.00	0.090	20	10	0.123	0.044	0.0369	0.0003	Nil	0.0004	17.18	10.25	94.27

Length of reaction zone = 2.75 inches. * Nil < 0.5 p.p.m.

Table 3 Coal Pyrolysis in an Argon/Hydrogen Plasma (Experimental Results)

Run No.	Coal sample No.	Power input (kW)	PF feed rate (g/min)	Gas analysis, % by volume						C ₂ H ₂ yield, % by weight of C in dry coal
				H ₂	CO	CH ₄	C ₂ H ₆	C ₂ H ₄	C ₂ H ₂	
1	2	8.1	0.044	2.050	Trace*	0.0039	0.0003	0.0051	0.0599	58.5
2		8.1	0.072	1.847	Trace	0.0033	0.0003	0.0051	0.0923	54.9
3		8.1	0.093	1.950	Trace	0.0034	0.0002	0.0056	0.1201	55.5
4		11.2	0.092	3.685	Trace	0.0077	0.0002	0.0205	0.1240	58.9
5		11.2	0.051	3.685	Trace	0.0074	0.0005	0.0134	0.0668	57.1
6		10.9	0.035	4.880	Trace	0.0083	0.0002	0.0076	0.0496	62.7
7		10.9	0.044	6.160	Trace	0.0090	0.0004	0.0125	0.0660	67.3
8		13.6	0.044	9.170	Trace	0.0139	0.0005	0.0105	0.0699	74.0

* Trace CO < 0.02%. Total argon flow in all cases was 30 N l./min.

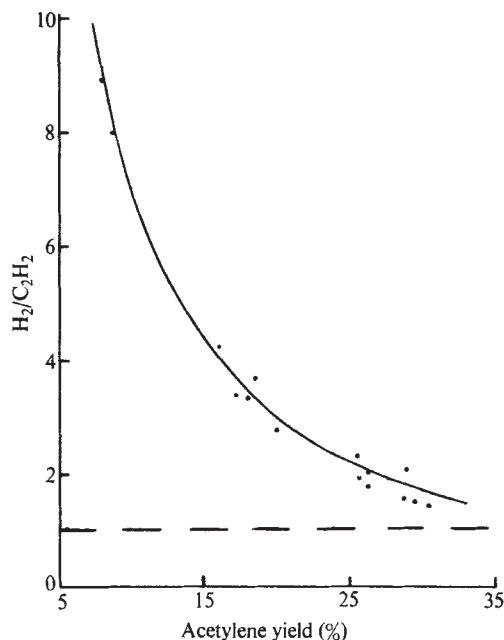


Fig. 4 Hydrogen-acetylene ratio as function of acetylene yield. Barnborough coal sample.

acetylene yield of 74% by weight on a carbon basis was obtained from the Barnborough coal—the highest yield of acetylene from coal yet reported. This work is being continued at Sheffield.

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BIOLOGICAL SCIENCES

Hydroxyguanidine—a New Antitumour Drug

RECENT observations have again drawn attention to a possible viral aetiology for certain types of cancer. Among these observations are: the presence of RNA dependent DNA polymerase (reverse transcriptase) in human leukaemic cells¹; the presence of viral particles in the milk of Parsi women of Bombay and the concurrent presence of reverse transcriptase

in the same samples of milk that contain the virus particles²; the leukaemic transformation of engrafted marrow cells *in vivo*³; and the induction of lymphoma and leukaemia in non-human primates with *Herpesvirus saimiri*^{4,5}. These observations suggest that for the "cure" of certain types of cancer, drugs with activity against oncogenic virus will have to be combined with currently used antitumour agents, or that interferon (or interferon inducers) with antiviral and antitumour activity will have to be used^{6,7}. Another alternative would be to combine the essential moieties of antiviral agents with the necessary moieties of molecules having antitumour activity in the hope that the resulting compound would have both activities.

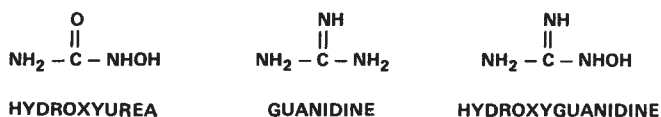


Fig. 1 Comparison of chemical structures.

I report here on the antiviral and antitumour activity of hydroxyguanidine (Fig. 1). Hydroxyguanidine combines the imino-group of guanidine, an antiviral agent^{8,9}, with the hydroxyamino group of hydroxyurea, a drug which has experimental and clinical antitumour activity¹⁰⁻¹².

Hydroxyguanidine sulphate $(\text{NH}_2\text{C}:\text{NHNHOH})_2 \cdot \text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$, MW 266.24) was used in these experiments and was dissolved in water shortly before use. Hydroxyguanidine was examined for *in vitro* activity against the Moloney sarcoma virus—Rauscher pseudotype M-MSV (RLV) by assaying for its effect on focus forming units and for *in vitro* cytotoxic effects (inhibition of cell growth) in four tumour lines: leukaemias L1210 and L5178Y, Novikoff hepatoma and Walker 256 carcinosarcoma¹³. In addition, it was examined for activity *in vivo* against four experimental tumours; mast cell P815, leukaemia P388, leukaemia L1210 and carcinosarcoma Walker 256. All tumours were inoculated intraperitoneally and treatment with hydroxyguanidine began 24 h after inoculation and continued until death or for 30 days. The animals were treated with intraperitoneal injections of hydroxyguanidine once a day and at least four dose levels of hydroxyguanidine were used in each experiment. Results are reported as percentage increase in median survival time over that of untreated controls.

Table 1 Activity of Hydroxyguanidine Sulphate against Various Experimental Tumours

Tumour	Range of doses tested (mg/kg)	Optimal daily dose (mg/kg)	% Increase in median survival time over that of controls
Mast cell P815	300–600	500	116
Leukaemia P388	300–600	500	145
Leukaemia L1210	200–800	600	90
Carcinosarcoma W-256	200–500	200	> 1,000*

* All rats at this dose level are alive and tumour free more than 5 months after inoculation.

The dose of hydroxyguanidine necessary for 50% inhibition (ID_{50}) of Moloney sarcoma virus as assayed by reduction in focus forming units as compared with controls was 2 µg/ml. Hydroxyguanidine also had cytotoxic effects against four tumour lines *in vitro*. The ID_{50} as assayed by reduction in cell growth at 24 h was 100 µg/ml. for leukaemia L1210 and leukaemia L5178Y and 25 µg/ml. for Novikoff hepatoma cells. The dose necessary for 50% inhibition of growth of Walker 256 carcinosarcoma cells *in vitro* at 48 h was also 25 µg/ml.

In addition to its antiviral and cytotoxic effects *in vitro*, hydroxyguanidine also has antitumour activity *in vivo* against various experimental tumours (Table 1). Hydroxyguanidine produced increases in survival time of 90% and 145% in mice bearing leukaemia L1210 and leukaemia P388 respectively. It was also active in mice bearing the mast cell tumour P815 and rats bearing Walker 256 carcinosarcoma. The effect of hydroxyguanidine against other oncogenic viruses and other tumours both *in vitro* and *in vivo* is under investigation.

However, it seems likely that moieties of other antiviral agents combined with moieties of antitumour drugs may well yield other compounds with potent dual chemotherapeutic activity.

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Repeated Denervation and Reinnervation of Skeletal Muscle

THE skeletal muscle in human muscular dystrophy shows marked degenerative changes while the central and peripheral nervous systems usually show no abnormality, apart from cerebral malformation underlying co-existing mental deficiency¹⁻³. In the late stages, there may be some loss of anterior horn cells in the spinal cord⁴. On the basis of these pathological findings, muscular dystrophy has always been considered to be a primary muscle disease. An inherited abnormality of the Bar Harbor 129 strain of mice shows similar pathological changes in the skeletal muscle and no central nervous system abnormality^{5,6}. Motor end plates are infrequent on the small atrophic fibres of the muscles, however⁷, and electromyography in these animals shows fibrillation potentials and high frequency discharges similar to those seen in human dystrophia myotonica and denervation⁸. Other findings suggestive of denervation are the reduction of frequency of miniature end plate potentials⁹, and the supersensitivity of the muscle to neostigmine and insensitivity to d-tubocurarine¹⁰. McComas and Mrozek¹¹ found direct evidence of a proportion of denervated fibres in murine muscular dystrophy.

Interest has developed recently in the trophic effects of nerves on muscle. In cross-innervation studies, the reinnerva-

tion of a "slow" muscle like the soleus by a nerve to a "fast" muscle such as the flexor digitorum longus or vice versa changes the histochemical and physiological properties of contraction of the muscle towards that of the reinnervating nerve¹²⁻¹⁶.

Recently McComas and his colleagues have developed a technique for measuring the number of motor units in the extensor digitorum brevis muscle of man¹⁷. In patients with Duchenne pseudohypertrophic, limb-girdle and facioscapulo-humeral muscular dystrophies, as well as dystrophia myotonica they found a 3-4-fold reduction in the number of motor units compared with normal controls¹⁸⁻²⁰. In the tibialis anterior muscle of dystrophic mice there was a similarly reduced number of motor units compared with controls²¹. The number of myelinated nerve fibres in the nerve to tibialis anterior was also reduced in these animals²². McComas *et al.* have advanced the theory that these various forms of muscular dystrophy may be due to a primary abnormality of the trophic influence of nerve on muscle^{18,19}. We have attempted to provide direct evidence for this theory by chronically impairing the trophic effect of nerve on a muscle. To achieve this, the gastrocnemius muscle of the rat was repeatedly denervated and allowed to become reinnervated by the original motor nerve fibres.

Adult white rats were anaesthetized with pentobarbitone followed by halothane and oxygen. The left medial popliteal nerve was exposed in the popliteal fossa using a sterile technique, crushed three times for a few seconds with smooth forceps (blade width 1.5 mm), and the wound closed with skin sutures. The right medial popliteal nerve was similarly exposed but the nerve was not crushed. Following recovery from the anaesthetic, animals showed weakness of plantar flexion of the left foot which recovered within 7-14 days of the operation. No weakness of the right side was seen. The operation was repeated every third week to a maximum of nine separate crushes. The same sequence of clinical weakness and recovery was seen each time. Animals receiving one to nine operations were killed 3 weeks after the last nerve crush. Eight animals were studied. Half of the medial heads of the left (experimental) and right (control) gastrocnemius muscles were placed in Susa fixative for light microscopy and the other half frozen in Arcton cooled in liquid nitrogen for histochemical staining and examination of the intramuscular nerves and motor end plates by the method of Namba *et al.*²³.

The right (control) muscles showed no abnormality; the "checkerboard" pattern of histochemical staining was preserved. The cross-sectional diameter of fibres of the left (experimental) muscle was approximately 70% of that of fibres from the right (control) muscle after the first nerve crush and decreased progressively to approximately 50% of the control in the animal receiving nine crushes (Fig. 1). In only one animal was there an area of grouped atrophy in the left (experimental) muscle after eight crushes. In the left gastrocnemius muscles of the other animals either the "checkerboard" histochemical pattern was preserved or all the fibres were of intermediate histochemical type. This was taken to indicate that most muscle fibres had been reinnervated by the nerve fibre which had originally innervated them by regeneration of the original nerve fibre within its basement membrane²⁴, rather than by the disorganized regeneration causing fibre type grouping which is seen following nerve transection¹²⁻¹⁶.

In the four animals receiving the largest number of crushes, rare foci of degeneration and regeneration were seen in the experimental muscle. The morphological picture, however, was in no way similar to muscular dystrophy in any of these gastrocnemii. In animals receiving the most crushes, a few intact nerve fibres were seen entering the muscle from the distal end. One rat was studied electrophysiologically 1 week after the eighth nerve crush. Stimulation of the left lateral popliteal nerve caused a small evoked action potential in the gastrocnemius muscle, while stimulation of the left medial popliteal nerve produced no activity. We concluded that a small amount of aberrant reinnervation from the lateral

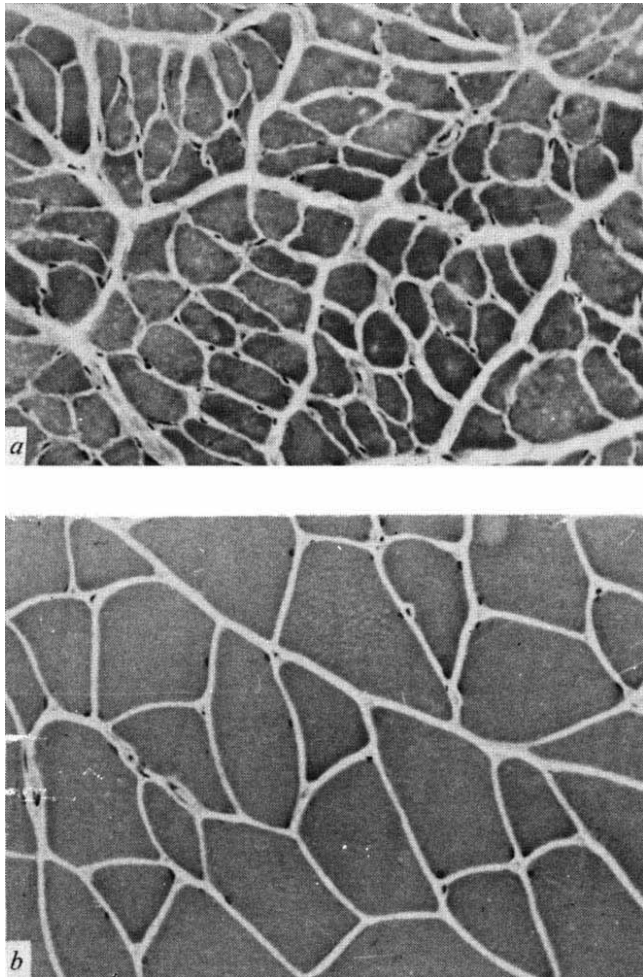


Fig. 1 *a*, Left (experimental) gastrocnemius muscle of rat receiving nine separate crush lesions of medial popliteal nerve in 27 weeks. Cryostat. Haematoxylin and eosin ($\times 244$). *b*, Right (control) gastrocnemius muscle of same animal at same magnification. Mean muscle fibre minimum transverse diameter of control muscle was $68 \pm 18.1 \mu\text{m}$ (mean $\pm$ s.d.), and of experimental muscle $29 \pm 9.8 \mu\text{m}$.

popliteal nerve had occurred in some of these animals. It is possible that this small degree of aberrant reinnervation could prevent the appearance of the dystrophic state in the muscle, since Elul *et al.*²⁵ showed that the trophic effect of the nerve may appear before neuromuscular transmission is established. This seems unlikely, however, for extensive muscle fibre atrophy did develop.

Muscle in long-standing denervation in man may show extensive myopathic changes^{26,27}. It is therefore possible that a more prolonged period of repeated denervation and reinnervation than studied here would reproduce the dystrophic state in the muscle. This appears unlikely since this study in the rat continued for six months, while in the mouse, at least, muscle fibre breakdown begins within a few weeks of birth⁵⁻⁷. This study therefore, in which the trophic effect of nerve on muscle was chronically impaired for more than 6 months to a sufficient degree to cause severe muscle fibre atrophy, does not support the theory that muscular dystrophy is due to impairment of this trophic effect.

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Effect of Odorants on Lipid Monolayers from Bovine Olfactory Epithelium

PLASMA membranes isolated from bovine olfactory epithelium containing large numbers of olfactory receptors cells are characterized by a high lipid, and especially phospholipid, content¹. Odorant molecules are lipid-soluble, and so this suggests that the interaction of odorant molecules with the lipid layer of the olfactory receptor membrane is important in olfactory reception. We have therefore examined the effect of various odorants on lipid monolayers from olfactory epithelium and propose a theory for the mechanism of olfactory reception.

The lipid composition of the whole homogenate of the bovine olfactory epithelium closely resembles that of the plasma membranes isolated from the epithelium¹. Lipids extracted from bovine olfactory epithelium were therefore used. The monolayers of the lipids were spread on the surface of Ringer solution, in which an aqueous solution of the odorant under investigation was injected with a microsyringe. Interaction of the monolayers with the odorant was examined by measuring the increase of the surface tension in the monolayers.

Fig. 1 shows the relation between odorant concentration in the subsolution and a surface pressure increase in the monolayers. The effect of the odorants on surface tension of the Ringer solution without the lipid monolayers was practically negligible in the concentration range studied. Concentrations

which give an identical surface tension increase in the monolayers differ greatly among the curves for various odorants.

Table 1 shows odorant concentrations which give a surface tension increase of 1.0 dyne cm^{-1} . For comparison, the olfactory thresholds of the odorants which are taken from the literature are represented in number of molecules of odorant per ml. of air. There seems to be a close correlation between concentrations giving an identical surface tension increase and the threshold concentrations of the odorants.

Our explanation is that the application of odorants to the monolayers brings about penetration of odorants into the monolayers and produces an increase of surface tension in the monolayers. Olfactory stimulation is induced by conformational change of the olfactory receptor membrane derived from adsorption of odorants to the lipid layer of the membrane. Considering the curve showing the relation between tension increase of the monolayers and odorant concentration to be linear in the concentration range giving a small tension increase such as below 1 dyne cm^{-1} , the following equation is written

$$\frac{1}{\alpha} = \frac{C}{kT}$$

where C is odorant concentration giving a surface tension increase of 1 dyne cm^{-1} , T is threshold concentration of odorants, α is surface pressure increase derived from adsorption of odorants at the threshold level and k is a factor to calculate molar concentration of odorant dissolved in aqueous mucus

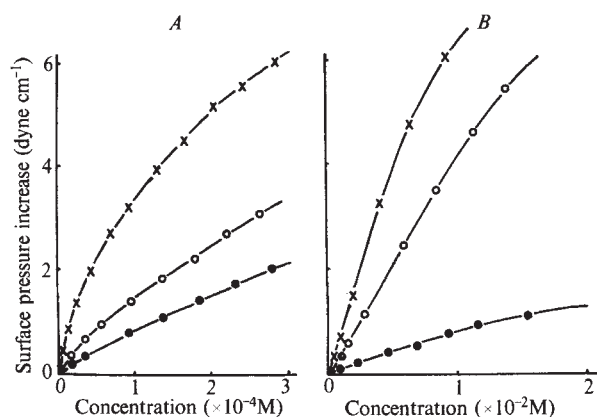


Fig. 1 Relation between odorant concentration and a surface pressure increase in the monolayers. The monolayers of the lipids were spread from a dilute solution ($0.3\text{--}0.5 \text{ mg ml}^{-1}$) in the extraction medium (chloroform-methanol, 2:1 v/v) on the surface of a Ringer solution containing NaCl 154 mM, KCl 5.6 mM and CaCl_2 2.2 mM and buffered to pH 7.3 with 20 mM $\text{NaHCO}_3\text{--HCl}$ buffer. The trough was made of 'Teflon'. To stir subsolution adequately, a trough with a deep depression ($170 \times 150 \times 10 \text{ mm}$) and a shallow depression ($230 \times 150 \times 0.5 \text{ mm}$) was devised. Both sections of the trough were filled with Ringer solution and the monolayers of the lipid were spread on the whole surface of the trough. After 10 min the monolayers were compressed to occupy only the surface area on the deep section by moving a 'Teflon' barrier from the right side of the shallow section to the left side. The 'Teflon' barrier was set to make a narrow clean area with about 5 mm width between the barrier and the right side of the deep room. The amount of lipid applied to Ringer solution was determined so that a surface tension of the monolayers gives 10 dynes cm^{-1} at the above compressed state. An aqueous solution of the odorant under investigation was injected in a Ringer solution with a microsyringe through the clean narrow area and an equal volume of a Ringer solution was removed from the subsolution. The odorant was distributed evenly by gentle stirring with a magnetic stirrer. Two minutes after stirring, the surface tension of the monolayers was measured using the vertical plate method². The water used in the present study was twice distilled in an all-glass apparatus and all reagents were analytical reagent grade. All measurements were made at $23 \pm 0.2^\circ \text{C}$. A, x, Menthol; o, coumarin; ●, isoamyl acetate; B, x, phenol; ○, 1-butanol; ●, 1-propanol.

covering the olfactory organ when gaseous odorant at threshold level is sniffed. The above equation can be changed into

$$\log T = \log C + \log \frac{\alpha}{k}$$

In Fig. 2, $\log T$ of the odorant is plotted against $\log C$. The points in Fig. 2 seem to lie almost on a straight line, the slope of which is 1. The odorants investigated in this present study are varied and may interact with the lipid membrane in different modes. But the fact that the linear relation was obtained between $\log T$ and $\log C$ reveals that the values of α/k are constant for different odorants. Olfactory perception is too rapid to be based on the diffusion of gaseous odorant into aqueous mucus⁷. Odorants seem to reach the receptor membrane through mucus by motion of air caused by breathing, since we smell only when we breathe⁷. Values of k therefore seem to be constant for different odorants, irrespective of the partition coefficient of odorant between the gaseous and aqueous phase. This reveals that α values, which are pressure increase derived from adsorption of odorants at threshold level, are not significantly different among different odorants.

Table 1 Odorant Concentrations giving a Surface Tension Increase of 1.0 dyne cm^{-1} and Threshold Concentrations of Odorants

	Concentrations giving a tension increase of 1.0 dyne cm^{-1} (M)	Thresholds expressed in molecules/ml. of air	References for thresholds
β-Ionone	2.4×10^{-7}	3.1×10^8	(3)
Skatol	1.4×10^{-6}	$1.6 \sim 1.8 \times 10^9$	(4)†
1-Octanol	2.0×10^{-6}	3.0×10^{10}	(5)
Menthol	1.7×10^{-5}	2.0×10^{11}	(5)
Heptanoic acid	2.0×10^{-5}	1.6×10^{10}	(4)†
Coumarin	6.0×10^{-5}	2.1×10^{11}	(5)
Isoamyl acetate	1.3×10^{-4}	4.2×10^{11}	(4)†
Methyl acetate	7.5×10^{-4}	1.6×10^{12}	(4)†
Ethyl butyrate	8.8×10^{-4}	1.5×10^{12}	(4)†
Methyl butyrate	1.2×10^{-3}	5.8×10^{11}	(4)†
Ethyl ether	1.2×10^{-3}	$6.1 \sim 8.1 \times 10^{12}$	(4)†
Acetaldehyde	1.6×10^{-3}	9.5×10^{12}	(4)†
Phenol	1.6×10^{-3}	$7.6 \sim 26 \times 10^{12}$	(4)†
1-Butanol	2.6×10^{-3}	8.1×10^{12}	(4)†
Acetic acid	5.5×10^{-3}	5.0×10^{13}	(3)
1-Propanol	1.3×10^{-2}	5.1×10^{13}	(4)†

* The middle values in the range were used to calculate $\log T$ in Fig. 2.

† The thresholds from ref. 4 were corrected according to Jones⁶.

We propose that olfactory stimulation is induced by conformational change of the receptor membrane derived from adsorption of odorants to the lipid layer of the membrane. Davies and Taylor^{5,8} have suggested, on the basis of studies on haemolysis of red cells by odorants, that a temporal puncturing of the olfactory receptor membrane by adsorption of odorants induces olfactory stimulation. Although our theory is partially connected with theirs, we do not postulate puncturing of the receptor membrane, and propose that non-odorous substances which adsorb to the receptor membrane may also act as stimulating substances for the olfactory receptor membrane, provided that the substances can get to the olfactory organ. In this context it is interesting that Gatchell⁹ observed that a fluid puff of the non-odorous substances to frog olfactory organ produced the electro-olfactograms which mimic those produced by a fluid puff of odorous substance. It is pointed out that there are two types of the receptor cells in the insect olfactory organ, that is, specialists which respond only to the specific odorant such as sex pheromone and generalists to

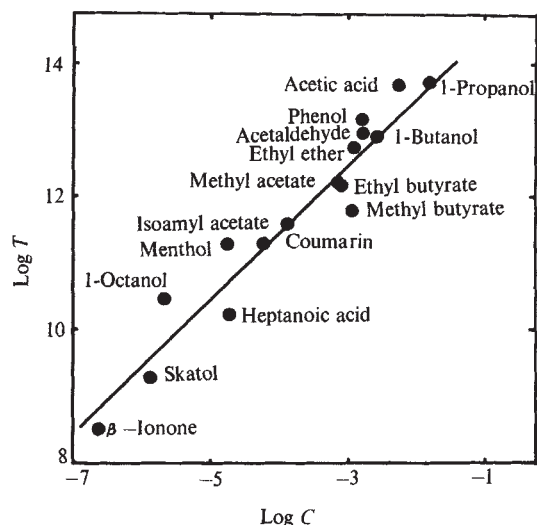


Fig. 2 Logarithm of olfactory threshold ($\log T$) plotted against logarithm of odorant concentration ($\log C$) giving a surface tension increase of 1.0 dyne cm^{-1} in the monolayers.

general odorants^{10,11}. The receptor molecules in the specialists may be proteins¹² which have a highly specific site to bind sex pheromone, while general odorants probably adsorb to the lipid layer of the receptor membrane as suggested in the present study.

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Release of Hormones in Insects after Poisoning with Insecticides

IN the insect, *Rhodnius*, many insecticides induce release of the diuretic hormone as they cause paralysis^{1,2}. It is possible that this hormone is not the only one released as a consequence of insecticidal action. A general release of neurohormones might be very important in the eventual death of treated insects. To test this idea, we have sought evidence of the release of other neurohormones after poisoning *Rhodnius* with various insecticides. We have taken as an example the

plasticizing factor which is normally released from nerve endings in the epidermis of the abdomen of *Rhodnius* as it feeds and which causes the abdominal cuticle to become extensible³.

Fifth stage larvae of *Rhodnius prolixus* from a large laboratory culture were taken 2–10 days after moulting, when they weighed 25–35 mg. Insecticide chemicals were either applied topically to the dorsum of the abdomen in 2 μl . of acetone, or injected into the haemolymph through a metathoracic leg in 15 μl . of saline⁴. The cut leg was sealed with a beeswax-resin mixture⁵ applied in a molten state with an electrically heated wire loop.

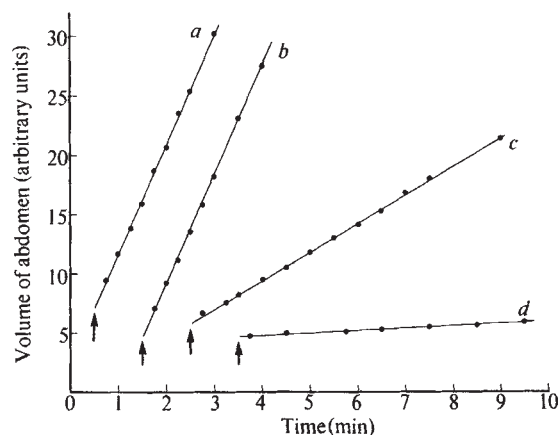


Fig. 1 Time courses of inflation of the abdomen of *Rhodnius*. a, A partly fed insect; b, an insect 200 min after poisoning with zectran topically applied at a dose of $175 \mu\text{g g}^{-1}$; c, an insect 165 min after poisoning with zectran; d, an unfed, untreated control insect. Inflation in each case was started at the point indicated by the arrow.

Where diuresis was followed, the anus was sealed with resin-wax mixture after the insect had been induced by handling to void its rectal contents. Rectal volumes could then be estimated in dissected insects by using an ocular micrometer to measure the diameter of the rectum which becomes spherical as it accumulates fluid.

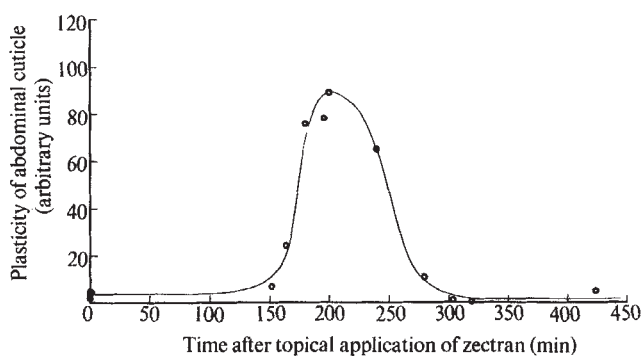


Fig. 2 The time course of plasticity of the abdominal cuticle in *Rhodnius* poisoned with zectran topically applied at a dose of $175 \mu\text{g g}^{-1}$.

To test the extensibility of the abdominal wall, insects were artificially inflated by blowing oxygen at a pressure of 10 cm Hg into the haemocoel through a hypodermic needle inserted into the abdomen through the anus³. The maximum width of the abdomen was measured with an ocular micrometer and a measure related to the volume of the abdomen was calculated by cubing the measured width. Plots of these values against

time yield approximately straight lines (Fig. 1) and the slopes of these lines were taken as measures of the extensibility of the abdominal wall.

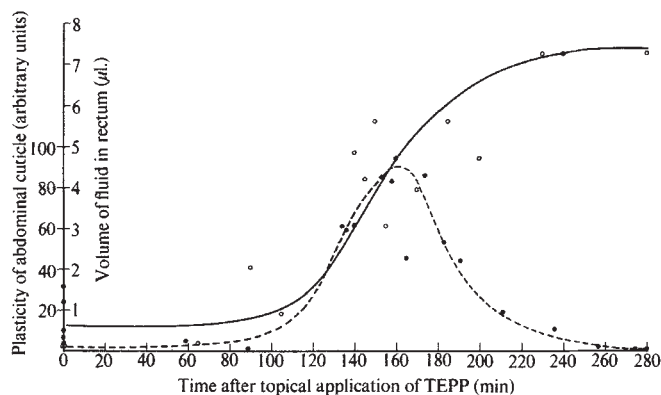


Fig. 3 The time course of diuresis (○—○) and of plasticization of the abdominal cuticle (●—●) in *Rhodnius* poisoned with TEPP topically applied at a dose of $160 \mu\text{g g}^{-1}$.

Rhodnius poisoned topically with the methylcarbamate, zectran, in a dose of $175 \mu\text{g g}^{-1}$ were examined at intervals over 7 h. A series of control insects was treated topically with acetone alone. Test inflations showed that the abdominal cuticle became plastic about 160 min after the insecticide treatment, reaching a peak value some 40 min later. Thereafter the cuticle became relatively inextensible again (Fig. 2). The insects had all succumbed to paralysis by the onset of plasticization and then remained paralysed. The acetone-treated insects neither became paralysed nor was their abdominal cuticle plasticized. A number of other insecticide chemicals also caused plasticization of the abdominal cuticle (Table 1). Representatives of each of the major classes of insecticide were found to induce plasticization. A similarly wide range of substances is known to cause the release of the diuretic hormone in *Rhodnius*^{1,2}.

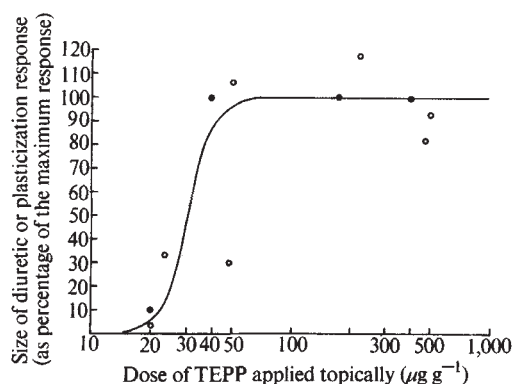


Fig. 4 Dose-response curve for the effect of topically applied TEPP on diuresis (○) and plasticity of the abdominal cuticle (●) in *Rhodnius*.

The time course of rectal filling and abdominal plasticization induced by a number of insecticides was followed. A typical result for insects poisoned with the organophosphate, TEPP, is shown in Fig. 3, which shows that diuresis and plasticization occur at approximately the same time. Another link between TEPP-induced diuresis and plasticization is the identity of the dose-response curves for the two effects (Fig. 4). The curve

shown is also identical to that for paralysis caused by the insecticide. Wherever paralysis was observed, plasticization and diuresis followed in due course. The coincidence in time of plasticization and diuresis as induced by TEPP (and, for example, amino-zectran) suggests that a similar chain of events precedes these two effects. In the case of DDT-induced poisoning, however, the two events are not simultaneous, plasticization of the abdominal cuticle preceding diuresis by about 2 h (Fig. 5). In the case of nicotine poisoning, diuresis precedes plasticization. In all cases of poisoning which led to paralysis, however, both diuresis and plasticization were always observed.

Table 1 Insecticides Tested and Found to Cause Plasticization of the Abdominal Cuticle

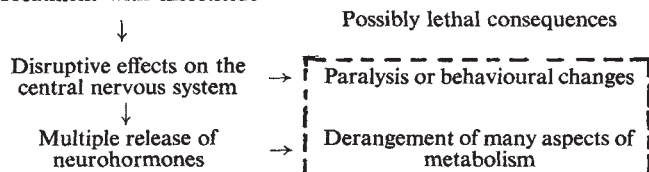
	Mode of application	Dose
Chlorinated hydrocarbons		
<i>p,p'</i> -DDT	Injection in suspension	$25 \mu\text{g g}^{-1}$
γ -HCH (lindane)	Topical	$500 \mu\text{g g}^{-1}$
Cyclodienes		
Dieldrin	Injection in ethanol/Ringer suspension	$50 \mu\text{g g}^{-1}$
Organophosphates		
TEPP	Topical	Various (see D-R curve, Fig. 5)
Carbamates		
Zectran	Topical	$175 \mu\text{g g}^{-1}$
Amino-zectran	Injection	$0.44 \mu\text{g g}^{-1}$
Botanicals		
Nicotine	Injection	$100 \mu\text{g g}^{-1}$

Diuresis induced by insecticide poisoning is due to the release of the insect's diuretic hormone^{1,2}. Normal plasticization of the abdominal cuticle during feeding depends on a localized release of a neurosecretory factor from the endings of the abdominal nerves³. That the plasticization which occurs in poisoned insects also involves these same abdominal nerves was shown by poisoning, with TEPP, insects whose abdomina had been partially denervated. Such operated insects later inflated asymmetrically, the innervated half-segments being plasticized, and hence stretched by the inflation, while the denervated areas remained unplasticized and unstretched. This result shows that plasticization induced by insecticides is mediated in the same way as that induced by feeding, the normal stimulus, and not by (for example) an alteration in the ionic balance of the haemolymph caused by the extensive diuresis which is occurring simultaneously. It is worth noting that the abdominal cuticle becomes plastic after poisoning to the same extent as it does after feeding naturally. Further proof that plasticization is not a consequence of diuresis in poisoned insects comes from the experiments with DDT-poisoned insects. In this case, although diuresis and plasticization both occur, the abdominal cuticle becomes plastic well before diuresis begins (Fig. 5).

It can now be concluded that a paralytic dose of insecticide will produce a release both of the diuretic hormone and of the plasticizing factor in *Rhodnius*, by the same pathways used in the natural release of these substances. The discovery that insecticide poisoning causes the release of at least two neurohormones in *Rhodnius* suggests that many insecticides may provoke a general release of neurohormones from the central nervous system of insects. It is easy to believe that this would have very damaging consequences for the insect and may indeed in many cases constitute the lethal step in insecticide action. This idea may explain why very many insecticides are found to affect the central nervous system either directly or

indirectly. The response to insecticide treatment which the present experiments suggest is the following:

Treatment with insecticide



Multicomponent schemes of insecticide action similar to this have been suggested before^{6,7}. The distinctive contribution of the work described here is to provide the first real evidence of multiple neurohormone release during poisoning in an insect. Precisely which component is the actual cause of death in any particular case will vary according to the species of insect and to its physiological state and the stresses imposed on it by the environment at the time of poisoning.

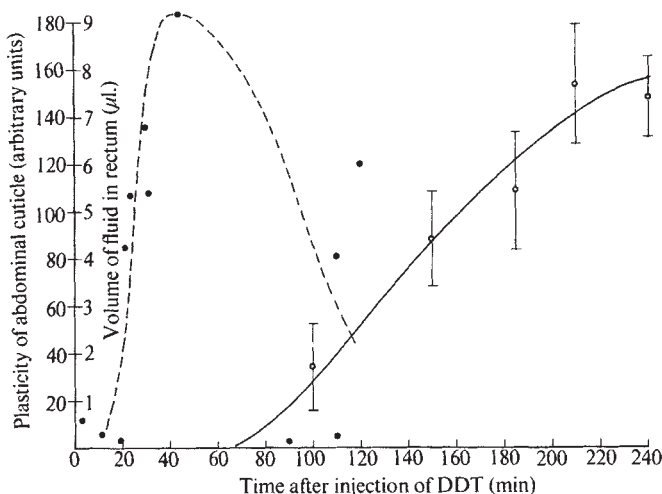


Fig. 5 The time course of diuresis (○—○) and of plasticity of the abdominal cuticle (●---●) in *Rhodnius* poisoned with DDT injected at a dose of $25 \mu\text{g g}^{-1}$. (The figures for the extent of diuresis were determined on groups of insects; the points on the graph represent mean values and the attached vertical lines the extent of twice the standard error of the mean.)

The possibility that some insecticides kill insects by provoking the release of their neurohormones has implications for the development of new insecticide chemicals. First, it suggests that pharmacological research on the insect central nervous system would be valuable, for it might reveal more effective ways of inducing general hormone release. Second, it suggests that compounds structurally similar to insect neurohormones might themselves be used directly as insecticides. They would have the advantage of being potent, specific and biodegradable.

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Sinapis alba, a Plant requiring a Single Long Day or a Single Short Day for Flowering

Sinapis alba (white mustard) will flower only in a regime of long days and short nights when the temperature is kept at 20°C , the relative humidity is 80% and illumination is provided by fluorescent white light (Phytor C.R.H.Lg. tubes) providing an intensity of $22,000$ to $28,000 \text{ ergs cm}^{-2} \text{ s}^{-1}$ at the top of the plants¹. In these conditions, 65 day old plants subjected from sowing to 8 h days (0830 h to 1630 h) can be induced to flower by exposure to a single long day beginning at 0830 h¹. The longer the photoperiod, the more complete is flower induction, with a maximal response after 18 h; in photoperiods shorter than 10 h flowering does not occur.

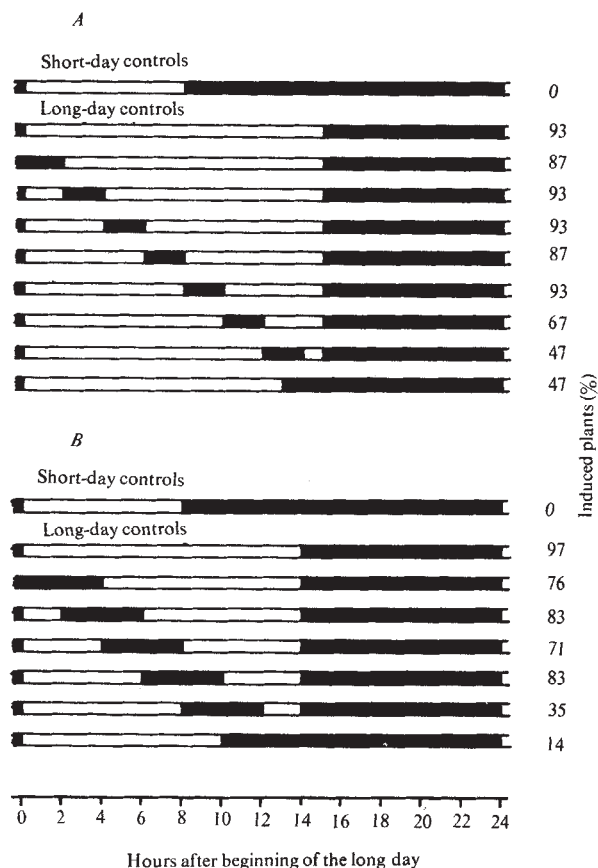


Fig. 1 Effect on the flowering response of 2 h (A) or 4 h (B) of darkness at different times during the inductive long day.

The experiments reported here were carried out on 65 day old vegetative *Sinapis*; they were replicated once and fifteen plants were used in each experimental batch for both experiments. After treatment, plants were returned to 8 h days for 2 weeks and apical buds were then dissected and classified as

vegetative or reproductive using the visibility of at least one flower primordium as the criterion of flowering.

We found, first, that 2 or 4 h of darkness (Fig. 1) provided at different times during the first 10 h of the single long day had little effect on flower induction. A period of darkness after the tenth hour, however, greatly reduced the flowering response. Thus continuous light does not seem to be necessary during the first 10 h of the long day, that is during the critical day, but after this it is essential for flower induction. This observation suggests that the moment of exposure to light has a considerable influence on the flowering response. Nakashima², using a long day duckweed, *Lemna gibba* G3, came to the same conclusion.

To test this inference, different sets of 65 day old vegetative plants were subjected to a single 8 h day at different times during a 40 h dark period beginning at 1630 h on 1 day and ending at 0830 h 2 days later.

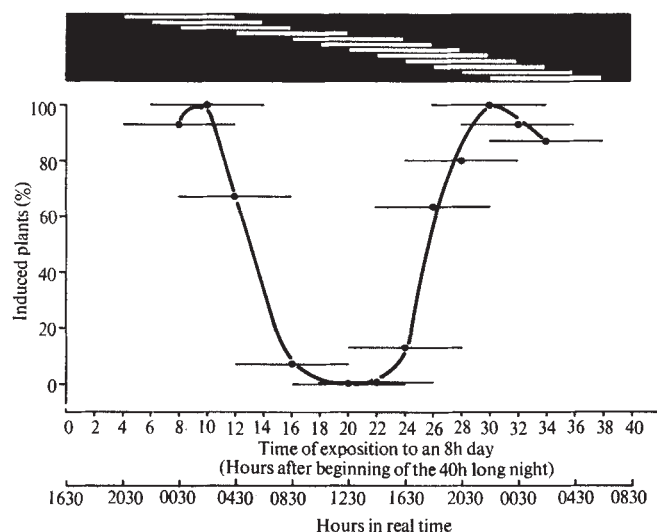


Fig. 2 Flowering response in plants exposed to an 8 h day (indicated as horizontal datum line) at different times during a 40 h dark period. Points correspond to the middle of the light period. Bars above the figure represent the plan of the experiment; they are drawn to scale of the abscissa. Results are plotted in terms of time after the beginning of the 40 h dark period and in terms of real time, that is the time of day in hours.

Fig. 2 shows that flowering could be induced by an 8 h day, but that the floral response depended considerably on the time of exposure to this short day. An 8 h day between the sixth and fourteenth hour after the beginning of the 40 h dark period or between the twenty-sixth and thirty-fourth hour induced full flowering while plants subjected to light from the sixteenth to twenty-fourth hour did not flower. This indicates that the floral response of *Sinapis alba* exhibits a cycle of sensitivity to light, with a period of about 20 h. This implies a circadian rhythm^{3,4}. The state (in the sense of Papenfuss and Salisbury⁵) during which light has a promotive effect on flowering (that is from about 1830 h to 0630 h in real time) and the state during which light is innocuous (that is from 0630 h to 1830 h in real time) could be respectively the photophil and skotophil phases of Bünning⁶. The fact that an 8 h day during the light promotive state can induce all the plants to flower indicates that light is required only during this state.

Thus it seems that when plants are induced by a single long day given from 0830 h, this day begins 2 h after the beginning of the light-innocuous state. As this state lasts about 12 h, it may be inferred that the time required to bring the plants to the beginning of the light-promotive state is about 10 h which corresponds exactly to the length of the critical day.

It would be interesting to know whether other long day and short day plants exhibiting a photoperiodic response to a

single cycle behave in the same way as *Sinapis*; at present, *Sinapis* is the only plant which can be induced to flower by a single long day or a single short day. The comparison of these two ways of inducing flowering in the same plant will be valuable in the study of processes occurring in the leaf and in the meristem during the transition from the vegetative to the reproductive condition.

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Dutch Elm Disease and Botanical Variation in English Elm

THE severe outbreaks of Dutch elm disease (*Ceratocystis ulmi*) in parts of southern England have not followed the pattern of earlier occurrences, and continue to cause concern. Features of particular interest are the possible effects of the disease in reducing the range of botanical variation in the English elm, and the extent to which the distributions of elm species have themselves influenced the intensity and extent of the outbreaks. It is generally agreed that the major division of the English elms is between *Ulmus glabra* Huds. (Ug), native in the north of England and more sporadic in the south, and the *Ulmus minor* and *Ulmus procera* complex. Until recently, *U. minor* has been referred to as *U. carpinifolia* Glad., and, together with *U. procera*, is probably native to southern Europe. The presence of the two species in England, where they seldom set seed, is most easily explained by human introduction from late pre-Roman time onwards. *U. minor* and *U. procera* are usually distinguishable in England. Hybrids between *U. glabra* and *U. minor* are well known, and Richens^{1,2} has suggested that hybrids may also occur between *U. procera* and *U. glabra* as well as between *U. minor* and *U. procera*.

Description of the botanical variation of English elm is complicated, but extensive biometric data are available from the studies of local populations of elm published by Richens¹⁻⁵. Based on 1,131 samples from these studies, representing practically the entire range of variation of elms in England, an analysis⁶ of the variation of eight leaf measurements has helped to clarify the taxonomy of the population. The great difficulty that taxonomists have encountered with *Ulmus* can be shown to result from the complexity of the situation in the field. Much parallel variation has occurred and many of the recognized variants are polyphyletic, but the English elm population consists of four principal taxa: *U. glabra* (Ug), *U. procera* (Up), *U. minor* (Um) and the *U. minor* × *U. glabra* hybrids (Umg). Of these, Um and Umg show the most extensive variation. It is possible to place individual trees within the main taxa and also within certain well-defined infraspecific groups within these taxa by discriminant analysis based on leaf measurements of five sub-distal leaves from dwarf shoots on stout branchlets.

During the survey of the incidence of Dutch elm disease in southern England recently carried out by the Forestry Commis-

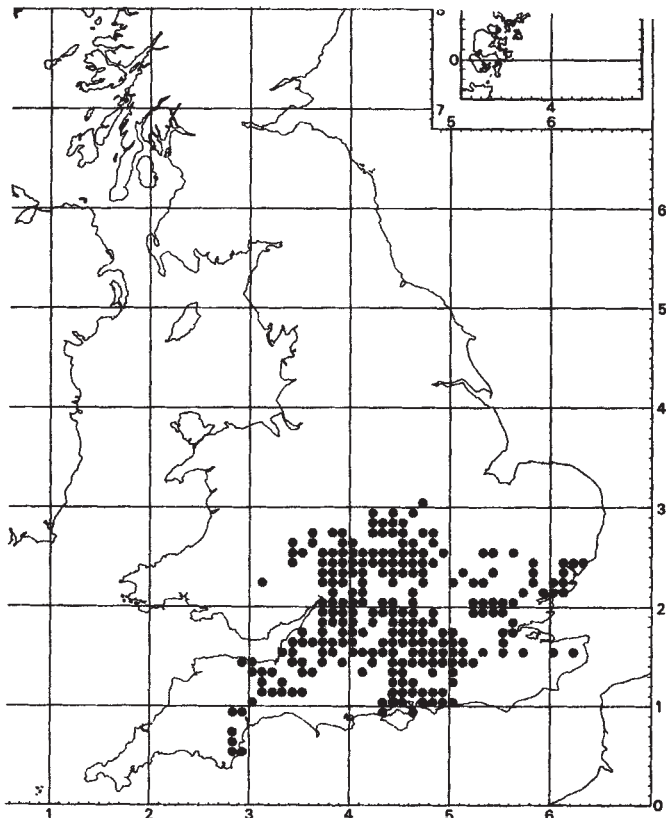


Fig. 1 Distribution of elm samples.

sion, sample leaves were collected from the first English elm encountered in the main plot of each 10 km grid square, thus providing a random sample of individual elms distributed over the area covered by the survey. Fig. 1 shows the 10 km squares from which the 260 samples collected were obtained. The same measurements as those used in the previous analyses were made on the five leaves of each sample, and the resulting averages referred to the discriminant analysis derived from the earlier studies. The numbers of individuals falling into the main taxa are given in Table 1.

Table 1 Allocation of Individual Trees to Taxa

Taxa	Total No. of trees	Healthy	Infected	Proportion infected
<i>Ulmus procera</i> (Up)	81	64	17	0.210
<i>Ulmus minor</i> (Um)	91	65	26	0.286
<i>Ulmus minor</i> × <i>Ulmus glabra</i> (Umg)	88	73	15	0.170
Total	260	202	58	0.223

From the total sample of 260 trees, eighty-one were identified as Up, and it is of particular interest that all of these trees belong to one of the three infraspecific groups which can be identified within this taxon. The range of botanical variation in the Up found in the area surveyed is therefore remarkably constrained. Ninety-one of the individual trees were identified as Um and eighty-eight as hybrids Umg. Very roughly, therefore, the samples were divided equally among these three taxa, with no observable differences in their geographical distribution. It seems likely that the field surveyors did not collect samples from Ug as they were asked to sample only English elm.

The incidence of healthy and infected trees in each taxon is also given in Table 1, and, although the differences between the proportions infected are not statistically significant, they

follow a pattern which is not unexpected, the hybrids Umg having a lower proportion infected than either Up or Um, and the Um having slightly higher proportions of infection than Up. The proportion of total trees infected (0.223) is an unbiased, if somewhat imprecise, estimate of the level of infection in the total area surveyed. At the 95% level of confidence, the percentage of infected trees lies somewhere between 17 and 28%. The numbers of individuals falling into the three infraspecific groups of Um found in the sample are given in Table 2. Again, although the differences between the proportions infected of these three groups are not statistically significant, there are suggestions that the differences may be of interest in terms of the resistance of these groups to infection by Dutch elm disease.

Table 2 Susceptibility of Infraspecific Groups of *Ulmus minor*

Infraspecific groups of <i>Ulmus minor</i>	Total No. of trees	Healthy	Infected	Proportion infected
D2 Small tooth, long petiole	57	41	16	0.281
D3 Small tooth, short petiole	20	12	8	0.400
D4 Asymmetric, long petiole	14	12	2	0.143
Total	91	65	26	0.286

This limited investigation establishes several important points about the susceptibility of parts of the range of botanical variation of English elm to infection by Dutch elm disease. First, it seems likely that 95% of all Up in this area belong to a single infraspecific group; they may, indeed, be from the same clone. They are, therefore, particularly susceptible to diseases or pests, and there is little possibility that resistant strains of this taxon can be expected to be found. Second, infection by Dutch elm disease is not confined to Up but occurs also in Um and in the hybrids Umg. Further verification is required of the suggestion that some groups of the more variable Um are more susceptible than others. Certainly, if resistant strains are to be found they will need to be looked for in this more variable taxon. Third, the hybrids Umg may possibly have a lower incidence of infection than the other two taxa, and, again, further investigation of the variability within this taxon seems desirable.

The situation does not look particularly promising for the Up, with their limited range of variation and apparently high susceptibility to the disease. Little resistance can be expected from natural variation within the taxon, and, if this part of the botanical variation of English elms is to be conserved, active measures to constrain the disease will be essential. Alternatively, it may be necessary to bank some of the vegetative material from the taxon in an area safely remote from Dutch elm disease, so that material will be available for repropagation of Up within the area once the disease has been constrained. The limited range of botanical variation within the taxon suggests that this would not be a difficult task.

Further work on the botanical variation of English elms and its distribution in Britain is, however, being undertaken in order to establish the relationship between this range of variation and the incidence and possible effects of Dutch elm disease.

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¹ Richens, R. H., *Forestry*, **38**, 225 (1965).

² Richens, R. H., *Forestry*, **40**, 185 (1967).

³ Richens, R. H., *Forestry*, **32**, 138 (1969).

⁴ Richens, R. H., *Forestry*, **34**, 47 (1961).

⁵ Richens, R. H., *Forestry*, **34**, 181 (1961).

⁶ Jeffers, J. N. R., and Richens, R. H., *Silvae Genetica*, **19**, 1 (1970).

BOOK REVIEWS

Strategy of Trees

Adaptive Geometry of Trees. By Henry S. Horn. Pp. xi+144. (Princeton University: Princeton, New Jersey, 1971.) £3.75.

Trees: Structure and Function. By M. H. Zimmerman and C. L. Brown. With a chapter on Irreversible Thermodynamics of Transport Phenomena by M. T. Tyree. Pp. xiii+336. (Springer-Verlag: Berlin and New York, 1971.) 72DM; \$19.80.

THE *Adaptive Geometry of Trees* is a rather unusual book with some stimulating and challenging concepts. It is concerned essentially with the development of a theoretical model based on light interception by tree crowns to explain forest succession from the colonization of open fields to a more or less stable climax.

Forest ecologists have long been aware that in the successional development of forest communities, species that are more tolerant of shade replace those that are less tolerant and that, as a general rule, the greater the degree of shade cast by a particular tree, the more shade tolerant its seedlings. The first concern of the author is to confirm these observations. This he does in a series of woodlands in central New Jersey representing different successional stages, by measuring the shade cast by different species, the ability of different species of sapling to grow beneath canopies producing different amounts of shade, and the age distribution of the stands. An account is given of the problems of light measurements in forests, their interpretation and details of the methods actually used.

Having established the significance of shade, with some useful discussion on the interpretation of shade tolerance, he then proceeds with his theoretical arguments. From considerations of the shading produced by single leaves, the photosynthetic efficiency of a leaf at different relative light intensities and the proportion of light penetrating a random array of leaves, he develops his concept of a leaf distribution "strategy". By comparing two extreme forms of distribution—a monolayer, in which the leaves are densely packed into a single

layer, and a multilayer, in which they are scattered through many layers—he is able to predict optimum leaf arrangements for various light and soil conditions which, he claims, are consistent with field observations.

The model is made quantitative by calculation of the photosynthetic rates of mono- and multi-layered distributions at different light intensities using an analogy with enzyme kinetics. Several predictions are then made concerning the specific composition and age distribution of forests at different stages of succession. These are checked by actual measurements of leaf distribution patterns in other, including tropical, forest successions.

The theory is then extended to predict the optimum shapes of tree crowns under different environmental conditions on the argument that the shape of the crown is part of the tree's strategy of light interception or successional status. The final chapter is devoted to a discussion of this adaptive strategy in relation to forest productivity, stability and diversity.

Most of the arguments are presented clearly enough, but the style is somewhat discursive so that the book is not easy to read; nevertheless, in view of the originality and ingenuity of the theory, it is well worth the effort. To comment effectively on the arguments, however, would require almost as much space as the book itself. Despite his apparent predictive successes, the author himself is well aware of, indeed he draws frequent attention to, the incompleteness of his model, the limitations of using a single factor as ubiquitous as light and the doubtful validity of applying the Michaelis-Menten equation of enzyme kinetics to calculate rates of photosynthesis. Perhaps the most appropriate conclusion to this review is provided in his preface—"the greatest homage that can be paid to an empirical theory is the constructive criticism that makes it obsolete at an early age".

Zimmerman and Brown's book is more conventional, and at a first glance promises to be not only a useful addition to the existing literature on tree physiology, but also a worthwhile contribution within the general field of whole plant

physiology. As implied in the title and amplified in the preface, its aim is to emphasize the relation between plant structure and function, for the study of which trees provide exceptionally good material. Furthermore, it is stated that the book is not intended to be encyclopaedic; in a field like tree physiology which includes an enormous number of empirical observations, accounts which stress principles rather than attempt to give full coverage of factual details are more than welcome.

Approximately half the book is written by Professor Brown and is devoted mainly to developmental and physiological aspects of tree growth. The account follows along more or less traditional lines with separate chapters on the primary growth of shoot and roots, on secondary growth and on the relationship between growth and form. This last chapter provides an opportunity to discuss such intriguing problems as ageing, apical dominance in tree crowns and the influence of gravity; brief reference is also made to environmental factors.

Treatment of the various topics varies considerably. The hormonal control of growth is discussed at some length and reasonably critically, whilst certain accounts, for example of long and short shoot development and of patterns of primary growth, provide rather more information than might have been expected in a book of this size. On the other hand, there are some notable deficiencies. For example, there is no worthwhile mention of leaf growth beyond the primordium stage, and to devote only one page to nutrient absorption by roots, and little more to mycorrhiza, does little justice to their structural-functional importance. Indeed, in the whole of this section, functional aspects receive rather less attention than might have been expected from the stated objectives of the book.

The two chapters by Professor Zimmerman on transport in xylem and phloem reflect a much more individualistic style of writing. Water transport is discussed largely on classical physiological lines and is particularly strong on the experimental side. Nowadays, with so much emphasis on thermodynamic

concepts, this classical approach may appear to be somewhat outmoded, but is not entirely unjustified if the main concern is with structure and function and if, as in the present case, thermodynamic aspects are dealt with in a later chapter. It is a pity, nevertheless, that so much space is occupied with attempts to calculate xylem conductivities from sap velocities obtained by the thermoelectric method; attractive though this method may be, the results cannot be accepted so uncritically. The account of phloem transport includes much of the author's well known research, and even though biased in favour of mass flow, it provides a well reasoned summary of the problem. To introduce some measure of impartiality, however, a short summary prepared by D. S. Fensom of his microfibrillar flow theory is included.

For those who are able to follow the rather complex arguments, the chapter by Dr Tyree on the steady state thermodynamics of translocation in plants is something of an unexpected bonus. He describes how the appropriate Onsager transport equations are derived, how they can be applied to interpret electro-osmosis and streaming potentials, and how, on the basis of energy dissipation, they can be used to evaluate the relative importance of electrical and pressure gradients in xylem and phloem transport.

The final chapter by Zimmerman on storage, mobilization and the circulation of assimilates is reasonably straightforward and returns the reader once again to the familiar world of classical plant physiology.

Though perhaps somewhat less original in its approach than might have been expected from its stated aims, the book as a whole differs sufficiently from previous publications in this field to merit serious attention. Many of the topics have been dealt with rather superficially, and several important aspects of structure-function relations have been omitted, but at least the authors have been reasonably successful in producing some readable accounts from a mass of factual, and frequently confusing, observations.

L. LEYTON

Keeping Books

Advances in Librarianship. Edited by Melvin J. Voigt. Vol. 2. Pp. xi+377. (Seminar Press: New York and London, 1971.) n.p.

THERE are a variety of *Annals* in most fields, librarianship being no exception; until recently, however, because this has been a fairly sterile discipline, several new *Annals* have appeared concurrently with the "break-out" mainly into library automation.

Advances in Librarianship has now completed its second cycle, the series purporting to cover "the field of library science in its broadest aspects . . . providing critical articles and surveys of specific aspects of the subject based on the published literature, research in progress, and developments in libraries of all types". The blurb goes on to claim that the "depth of coverage results in surveys of advances in the field that will be permanently useful in orienting librarians and students". This is, of course, difficult, for in any *Annual* cycle the probability that a subject has reached maturity within that cycle is low. Topicality and permanence are not good bedfellows and the current volume of *Advances* illustrates this as well as most other *Annals*.

One fairly uniform shortcoming of the nine sections which comprise this volume is the concentration on North American experience. For example, in the first section, Budington ("Access to Information") acknowledges the rest of the world by a passing reference to a three page British review, published in 1965. This is a pity for, although historical and descriptive reviews are of limited value in themselves, the effect of different requirements and economic circumstances on a problem can cause both objectives, methods and results to be markedly different.

In contrast, however, Bishop ("Information in Medicine") covers his subject as uniformly as the published literature permits.

Bosseau ("The Computer in Serials Processing and Control"), although treating the "rest of the world" in a somewhat cavalier fashion, provides detailed descriptions of some generalized systems, although one wonders whether such detail is appropriate in this volume. In contrast, Veaner ("Micro-publication") covers his subject, if anything, too compactly.

Beasley ("The Changing Role of the State Library"), in a section of interest only perhaps to American readers, observes that the role of State Libraries is changing and will continue to change, and concludes that, because they change, they are more innovative than other libraries. Monroe ("Reader Services to the Disadvantaged in Inner Cities") is also probably only of interest to American readers, whereas in contrast Schrader ("Armageddon in International Copyright: Review of the Berne Convention, the Universal Convention, and the Present Crisis in International Copyright"), while concerned predominantly with the American viewpoint, provides an extremely lucid and attractively written exposition of her subject.

There is also a section by Starr ("Oral History: Problems and Prospects").

On working through this volume, one

is left with the feeling that a number of interesting topics had been covered without much uniformity of presentation or level. One is left with a vague unease as to whether all the subjects covered are in fact ripe for review. It is also difficult to envisage a reader who would be equally interested in all the sections. This volume is certainly ideal reading for any librarian wishing to familiarize himself with sufficient background and jargon before attending an interview for a library post in North America.

N. S. M. COX

Kinetic Isotope Effects

Isotope Effects in Chemical Reactions. Edited by Clair J. Collins and Newell S. Bowman. Pp. xi+435. (Van Nostrand Reinhold: London, August 1971.) £11.25.

THE effect of isotopic substitution on the rates of chemical reactions was first observed and qualitatively explained in terms of zero-point energy soon after the discovery of deuterium in the early 1930s. The modern treatment of the subject by Bigeleisen and by Melander around 1950, and subsequent developments, retain much of this early idea.

The measurement of kinetic isotope effects, at first with deuterium and later with heavier isotopes, has become a powerful method in the investigation of reaction mechanisms. Early work was exclusively concerned with effects of deuterium substitution at a bond which is expected to be broken in the rate-limiting step. The rate changes are large in this case and their presence or absence identifies the rate-controlling process.

More recent applications have emphasized the information provided by the actual magnitude of the effects. Advances in experimental technique have also made the measurement of secondary hydrogen isotope effects easier. The mechanistic interpretation of these more quantitative results requires a more sophisticated theoretical analysis, which has become feasible with the development (chiefly by Wolfsberg and Stern) of computational techniques based on Bigeleisen's theory. The book under review contains five essays on this topic, and it could aptly be subtitled "Variations on a Theme by Bigeleisen". The distinguished authors give an introductory account of the theory (Van Hook), a more specialized and more personal treatment of the same topic (Thornton and Thornton), a discussion of kinetic secondary deuterium isotope effects in aliphatic nucleophilic substitution (Shiner), a treatment of the same topic from the point of view of a different laboratory (Sunko and Borčić), and a survey of kinetic heavy-atom isotope effects (Fry).

A sixth contribution provides a counter-theme, isotope effects in biological systems (Katz and Crespi): it contains some fascinating and almost totally unrelated material.

The quality of the contributions, which the distinguished senior editor and his colleague succeeded in attracting, is excellent. However, one cannot help wondering whether the volume which emerged is quite the one that was intended or whether someone oversimplified its title. One accepts that there was bound to be selection in what could be included in a single volume. But the general title of the book would lead the purchaser to expect a representative selection of isotope effects in chemical reactions. He would be disappointed in that respect. The reactions discussed are all taken from organic chemistry, and it is therefore almost inevitable that isotope effects on rates are considered much more fully than those on equilibrium constants. These restrictions are regrettable, especially in view of overlap between several of the contributions. Most chemists are at least aware that kinetic isotope effects provide useful information in organic chemistry. The contributions which isotope effects have already made to inorganic chemistry and the great scope that exists there (including, in that context, the chemistry of organo-metallic and coordination compounds) and in geochemistry are not so well known. Isotope effects on equilibrium constants (not only for acid-base equilibria in solution, which are reasonably excluded) promise to become an increasingly important tool in the study of interactions in the condensed phase. They are of practical importance to the production of isotopes.

In brief, this is an invaluable book for those already dedicated to the study of kinetic isotope effects in organic reactions for whom it will be essential reading. It is more doubtful whether it will do much to stimulate interest outside the circle of initiates and thereby lead to a wider appreciation of the powerful methods and beautiful theory of isotope effects. A fine volume has been produced: an opportunity has been missed.

V. GOLD

Polyamines

Introduction to Polyamines. By Seymour S. Cohen. Pp. ix+179. (Prentice Hall: Englewood Cliffs, New Jersey, 1971.) n.p.

SEYMOUR COHEN has been studying polyamines for a number of years and this book comprises four lectures that he gave on the subject at the Collège de France. Their publication, although

valuable as a summary of present knowledge, does have a didactic purpose because the author believes that polyamines constitute an underrated group of compounds. The book begins with an interesting description of the discovery and characterization of polyamines. Subsequent chapters are concerned with polyamines in prokaryotes and eukaryotes and their possible roles in cell physiology and, finally, with the molecules as organic cations in relation to nucleic acids.

Studies with mammalian systems have shown what seems to be a stoichiometric relation between polyamine concentration and the RNA contents of the cells. Stimulation of cell growth, and hence RNA synthesis, is accompanied or preceded by the synthesis of polyamines, a process which itself requires prior synthesis of the specific enzymes involved. With respect to bacterial physiology, Cohen himself has been concerned to try and relate changes in polyamine content and synthesis to concomitant changes in RNA metabolism. But it is fair to state that we still do not know if polyamines, present in all cells in millimolar concentrations, function solely as general cations, possibly contributing in addition to maintenance of the intracellular pH, or whether they have specific roles in relation to nucleic acid structure and function. This book should stimulate further interest in polyamines, thus contributing to the solution of the problems presented by the author.

G. TURNOCK

Roots of Chemistry

Teaching the History of Chemistry. Edited by George B. Kauffman. (A Symposium, San Francisco, California, April 1968.) Pp. 222. (Akademiai Kiado: Budapest, 1971.) £3.25.

THOSE who hold almost any view of how, when, or whether the history of chemistry should be taught will find support for it in this volume, which consists of eighteen papers read at a symposium at a national meeting of the American Chemical Society, and six other papers. They range from descriptions of the courses offered in particular colleges or countries, through general recommendations, to contributions to the history of chemistry or its historiography. The most apparent division between the authors is that some are chemists interested in history while others are historians whose field is the history of chemistry.

Chemists have long been interested in the history of their science, and Dr Solov'ev from Moscow indicates how in nineteenth-century Russia two differ-

ent interpretations of the past were used by opponents and supporters of structure theory, both claiming to be in the main stream. Most participants agree that chemistry used to be taught historically, but is now taught logically; and to many of the chemists courses in the history of chemistry bring a unity to the subject by indicating the common roots of its different branches, bring awareness of the process of discovery, and suggest that what is now taken for granted may in the future be exploded. Some urge separate courses in the history of chemistry, while others believe that chemistry will cease to seem colourless and over-factual when its presentation is enlivened with anecdotes and case-studies; we even find one lively account of a class being guided to discover phlogiston. Arguments can be found here for teaching history early in the course so that the student at once gains in perspective, and for teaching it late so that he knows a fair amount of chemistry already. Some authors see it as essential to a proper understanding of the concepts and methods of present day chemistry, while for others it is a valuable liberal element to be fitted in with economic and political history to broaden the chemist's outlook. But beneath all this there is a certain pessimism; as one author puts it, "the attitude of most chemists is one of indifference to anything so clearly expendable as this luxury item".

The historians, who are unlikely to be teaching only the history of chemistry and very unlikely to be teaching only chemists, take a rather different view. To them histories of chemistry written by and for chemists tend to seem parochial, in that they often ignore other sciences, and Whiggish in that they concentrate on the winning side in all past disputes. Attempts are made here: to seduce us into looking back at chemistry before Boyle; to integrate the history of chemistry with other branches of history; to remind historians of science that chemistry is not a branch of physics; and above all to make us pursue—and presumably teach—the history of chemistry for its own sake and not because it is useful for something else. While several of the chemists recommend case-studies to illuminate such philosophical points as the relation of facts to theories, one of the historians, Dr Tredgove, suggests that philosophers of science have nothing useful to say to the historian of chemistry, and that the history of chemistry has been distorted by concentration on philosophically-interesting but not very important events like the overthrow of the phlogiston theory. The symposium was, in short, clearly worth printing—it is a pie from which there are many plums to be pulled.

DAVID M. KNIGHT

Birds

The Status of Birds in Britain and Ireland. Edited by D. W. Snow. Prepared by the Records Committee of the British Ornithologists' Union. Pp. xviii+333. (Blackwell: Oxford, London and Edinburgh, 1971.) £3.75.

THIS work is the greatly improved successor to a series of editions of the so-called "British List" issued under the same auspices from 1883 to 1952. The whole concept of an "all-or-nothing" list has been criticized as unscientific; now a beginning has been made towards dividing the species into categories. In my opinion the general category "A" is still too wide; but there is a welcome approach to subdivision in the use of standard indications of status and abundance. This time, the members of the responsible committee have not set themselves up as arbiters on questions of taxonomy and nomenclature but have wisely followed specified authorities.

The great value of the book lies in the fuller information now given about the world distribution of each species and, still more, in the carefully ascertained details of current status in the British Isles, including internal incidence, abundance and movements. The result is an up-to-date picture of our avifauna which should well serve current needs and also provide a base-line for future studies.

The publication is authoritative not because it is "official" but because it represents the labours and corporate judgments of a band of experts over several strenuous years. They are to be congratulated on the outcome of their labours. The volume is pleasantly produced; and each familial section is headed by a drawing of a selected species by Robert Gillmor.

A. LANDSBOROUGH THOMSON

Taxonomy Rationalized

Mathematical Taxonomy. By Nicholas Jardine and Robin Sibson. Pp. xviii+286. (Wiley: London and New York, September 1971.) £6.

THIS is an important book. The authors have contributed substantially to numerical taxonomy in recent years and in this book bring together and organize much of their published work as well as advancing several important new concepts. It is a pity, therefore, that the organization and presentation of the material have not been more successful. Numerous new terms are introduced throughout the book, often without adequate initial definition. Jardine and Sibson frequently use esoteric terms and abbreviations with little mnemonic value

(examples are D-dissimilarity, B_k clustering, C_u methods) which will not help readers in assimilating the material. The development is highly technical. Numerical taxonomists will need to spend considerable time working through the material but their efforts will be richly rewarded. Even where they do not agree with some of the authors' assumptions or conclusions, the new insights presented will be of considerable value in testing their own ideas. I can attest to the seminal effect of this book on my colleagues.

The book is divided into three main sections and appendices. The first deals with dissimilarity measures, the second with clustering methods and the third discusses the principles of mathematical and biological taxonomy. The authors arrive at an information theoretical similarity measure and recommend single link clustering as the method of greatest mathematical appeal, while realizing its serious drawbacks. This latter recommendation leads me to retain some reservations about the conditions laid down by Jardine and Sibson for clustering methods.

The third section is a gem. Nowhere have I seen the problems of modern biological taxonomy dealt with so clearly in so limited an amount of space and with such good sense. I am only fearful that its placement as the third part of a book which is highly mathematical in its first two parts will keep it from its deserved large audience of biological taxonomists, who may be apathetic or inimical to the earlier two parts. It is clear that the authors belong to a new generation. None of the philosophical and emotional problems of earlier taxonomists are evident in the discussion. The absurdities of biological species (*sensu* Mayr and Dobzhansky), cladism (*sensu* Hennig), or phylogenetic weighting (*sensu* Mayr) are exposed as virtually self evident. Extreme pheneticism is equally criticized. The authors conclude that for most supraspecific groups phenetic taxonomy is probably the best system and that at the infraspecific levels hierarchies should be avoided.

Many of the appendices might have been omitted. The Fortran listings of computer programs are of little use because they use machine language sub-routines. They are also far too long for reproduction by keypunching, especially in view of the fact that they and certain statistical tables developed by Jardine and Sibson are reproduced so poorly as to make them hard to read. Two examples of actual classifications carried out by the methods of these authors are useful but not detailed enough. It will take fairly accomplished numerical taxonomists to compare these methods usefully with other established techniques.

In spite of some of these shortcomings the significance of this book for the future development of taxonomy should be obvious to any serious reader.

ROBERT R. SOKAL

Polymer Mechanics

Mechanical Properties of Solid Polymers. By I. M. Ward. Pp. xv+375. (Wiley: London and New York, December 1971.) £7.

PROFESSOR WARD's book is a welcome addition to the literature on the mechanical properties of polymeric materials, and reflects the growing interest in polymers as engineering materials. Although there have been previous books on the same general topic, this volume introduces a more rigorous treatment which will be welcomed both by those who teach the subject and those engaged in the areas of research or application.

The coverage is comprehensive, with chapters on structure, the rubber-like state, linear visco-elasticity, visco-elastic measurements, mechanical relaxations, non-linear visco-elasticity, anisotropic behaviour, yield and fracture. Some of these topics, of course, individually form the subject matter of established texts, and readers familiar with those books may not gain much that is new from the necessarily restricted coverage of a chapter or two in the present volume. To criticize the book on that score would be to miss its point, however. Professor Ward has provided one of those single-authored, synoptic treatments which are at once both rare and valuable. As an exposition of basic principles; as a summary of current knowledge; as a teaching manual and as an introduction to polymers for the scientist or engineer not trained in the field, the book fully achieves its objectives.

The author's viewpoint is strictly a continuum one. That is to say that solid polymers are considered almost exclusively as continuous media or else as homogeneous molecular assemblies. There is therefore little treatment (except for a few paragraphs in the "structure" chapter and elsewhere) of polymer morphology and its effects on mechanical properties, which can be profound. This omission is clearly deliberate, and it must be agreed that a polymer equivalent to a physical metallurgy or mechanical metallurgy text calls for another book rather than an expansion of the present volume.

It would have been valuable to have had a short bibliography, or suggestions for further reading, at the end of each chapter in addition to the references.

The book is very readable and well produced with good diagrams, and the mathematics are set out clearly.

E. H. ANDREWS

CORRESPONDENCE

Soft-centred Earth

SIR,—In the article "A Soft-centred Earth" (*Nature*, 235, 304; 1972), your correspondent appears to be implying that the detection of seismic pulses reflected from the inner core boundary announced by Engdahl *et al.* at the 1970 meeting of the Seismological Society of America was a novelty. In the interest of accuracy, and without diminishing in any way the accomplishment of Engdahl *et al.*, let me point out that more than 10 years ago Caloi (*Geophys. J. Roy. Astron. Soc.*, 4, 139; 1961) reported the detection of a PKiKP phase in records of Aegean earthquakes ($\Delta < 20^\circ$) obtained at Tolmezzo (Northern Italy). The conclusion he offered was that "The existence of a reflecting surface, as a boundary of the inner core, is a proof of the solid state of the inner core itself". His results were cited by Bullen (*An Introduction to the Theory of Seismology*, 3rd ed., 221; 1965), and therefore cannot be said not to have been presented to a wide audience of seismologists.

Yours faithfully,

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Ottawa

Concorde

SIR,—I write to comment on the passage in your issue of *Nature* (234, 372; 1971): "In other words, the Concorde has helped to demonstrate that it can only be a matter of time before supersonic aircraft are in regular airline service, providing passengers with the immense convenience of faster long-distance journeys and providing airlines with profits commensurate with the service they will be able to provide." Surely Concorde has demonstrated no such thing. What has been shown so far is that a supersonic airliner is probably feasible from the limited viewpoint of aeronautical engineering and that sonic bangs from such large aircraft are not tolerable as a daily event for humans. It does not follow that restricting bangs to oceans is free from objection, or that there can ever be profits from flying

such expensive aircraft without boom corridors overland. It is impossible to fly from London to Sydney or Tokyo without flying long distances over inhabited countries, and a bang is just as disturbing to an individual irrespective of whether he lives in a sparsely or densely populated place.

A number of other issues each of which on its own could put an end to commercial supersonic flying are still to be resolved. Who, for example, has refuted Professor Harold Johnston's hypothesis of the effects on ozone by supersonic transport exhaust? The *ad hoc* review panel formed by the National Academy of Sciences to consider this matter released a report in December which states "... there appears to be general agreement that Harold Johnston's conclusions as reported in his paper, 'Reduction of Stratospheric Ozone by Nitrogen Oxide Catalysts from SST Exhaust', are credible ... and that the possibility of serious effects on the normal ozone content cannot be dismissed ...". This, sir, contradicts your own view that "nobody is seriously worried about the effects of exhaust gases on the stratosphere ...".

One must expect optimism for supersonic airliners from the manufacturers of Concorde, but caution seems more appropriate from a scientific journal.

Your faithfully,

NEVILL MOTT

Cavendish Laboratory,
Free School Lane,
Cambridge

Atmospheric Mystery

SIR,—I would greatly appreciate comment on my observation of the following event.

I was standing on top of the Puy Mary, 1,787 metres high, the highest of the volcanic cones in the range of the Cantal mountains. To the north, about 1–2 miles away, I saw lightning coming out from a black bank of clouds and heard the thunder about 5–6 s later. However, I felt a strong blast of hot air reaching me before I could hear the thunderclap. This happened several times in quick succession, though I did

not time the length of the intervals between each lightning.

I think I am right in saying the blast, which was fairly strong, was the aftermath of the last lightning but one. It was almost silent and no doubt travelled at less than the speed of sound.

I have been near thunderstorms often enough in my life, in the Alps and on the plains, but this blast of hot air was something new to me, and I have not met anybody who had made a similar observation; hence my request for comment.

Yours faithfully,

L. H. WORTH

14 Clare Lawn Avenue,
East Sheen,
London SW14

Avery *et al.*

SIR,—I have before me Peyton Rous's copy of the reprint of the article by Avery, MacLeod and McCarty recently discussed by H. V. Wyatt (*Nature*, 235, 86; 1972). There can be little doubt that Avery gave this reprint to Rous at the time of its original appearance. On it Rous wrote, as an instruction to his secretary, "Please file under genetics". She did.

Your faithfully,

PAUL F. CRANFIELD

The Rockefeller University,
New York,
New York 10021

Bertrand Russell

SIR,—I am writing, with the cooperation of the Bertrand Russell estate, a major life of the late Bertrand Russell, and would be grateful to hear from any of your readers who have correspondence, photographs or information likely to be of use to a biographer.

Any material sent to me at the address given below will be returned without delay.

Yours faithfully,

RONALD W. CLARK

10 Campden Street,
Kensington,
London W8

Obituary

Ernst Krenkel'



ERNST TEODOROVICH KRENKEL', one of the leading pioneers of Soviet polar exploration, died suddenly on December 8, 1971.

Krenkel' began his work in the Arctic in 1924, as a member of one of the earliest Soviet polar research teams, at the station on Matochkin Shar. He played a leading part in the organization of the observatory on Franz Josef Land, and, during the 1920s and '30s, took part in a number of Arctic expeditions, including the international expedition on the Zeppelin dirigible.

In 1932 he took part in the expedition aboard the icebreaker SS Aleksandr Sibiryakov, which made the first single-season journey (July 28–October 1) through the North-East Passage, using the route north of

Severnaya Zemlya, and demonstrating the feasibility of direct shipping in the Soviet Arctic.

The following year he again sailed in a North-East passage expedition aboard the SS Chelyuskin, an ordinary cargo-passenger vessel. This expedition was intended to demonstrate that summer navigation of the North-East Passage was a commercial proposition. The Chelyuskin had apparently completed her voyage by November 1933 when Krenkel', who was in charge of radio communications, sent back the message: "We have sighted the Bering Straits". But six hours before their estimated time of arrival in the Straits, the Chelyuskin was trapped in heavy pack ice and began drifting slowly north and west, back into the Arctic Ocean. In February 1934 she sank, and the whole party of 120 men, 7 women, and a baby born on the voyage were left stranded on a drifting icefloe. Using radio equipment, which he afterwards described as being "of the most ordinary kind" which frequently "tried to go on strike", Krenkel' managed to keep in daily radio communication with the Wellen Island Base, and to supervise the logistics of the airlift which, over the course of the next two months, slowly evacuated the whole expedition. He himself was on the last flight out, on April 13, 1934.

Three years later, Krenkel' was adrift again on an icefloe, this time as part of the first of the Soviet North Pole drifting expeditions. This series of expeditions, which continues to the present day, is intended to study drift movements of the Arctic ice, and to carry

out a wide range of high-latitude research. The North Pole-1 team were flown in to an icefloe as close as possible to the Pole itself, and drifted slowly south for some nine months. Krenkel' was in charge of research into radio communications in high-latitude conditions, and also acted as communications officer for the party, his Chelyuskin experience proving most valuable for this purpose.

After the successful return of the expedition, Krenkel' was employed in administrative posts dealing with Arctic research—in the Chief Administration of the Northern Sea Route and the Chief Administration of the Weather Forecasting Service. In the last years of his life, he was head of the Scientific Research Institute of Hydrometeorological Instrumentation of the Weather Forecasting Service of the USSR. He continued to interest himself in problems of radio communications in Arctic conditions, and pioneered the use of various short-wave devices for this purpose.

In addition to a number of works of general interest, he wrote and lectured widely on problems of Arctic research. His chief publications include contributions to *The Voyage of the Chelyuskin* (1935) and *Proceedings of the Drift Station North Pole* (1940). With I. D. Papanin, the leader of the expedition, he wrote the official report of the expedition, *Nine Months on the Drifting Station North Pole*, which he supplemented by his personal *Diary* (1940), a detailed and witty account of the daily life of the expedition, illustrated with talented and often amusing sketches.

Announcements

Miscellaneous

Professor S. S. Stevens, Harvard University, has been awarded the Rayleigh gold medal of the **British Acoustical Society**.

The **Edinburgh Geological Society** has awarded the Clough medal to **Dr James Phemister**, for his work on the geology of Scotland and the North of England.

Dr V. C. Barry, director of the laboratories of the Medical Research Council of Ireland, has been elected president of the **Royal Irish Academy**.

International Meetings

April 24–25, **Combustion Problems in Industry and Agriculture**, Seattle, Washington (Professor R. C. Corlett, Department of Mechanical Engineering, Mail Stop FU-10, University of Washington, Seattle, Washington 98195, USA).

April 26, **Testing and Evaluation in Laboratory Animals**, London (B. Hunter, Huntingdon Research Centre, Huntingdon).

May 1–3, **Bioengineering**, Omaha (Rocky Mountain Bioengineering Symposium Inc., PO Box 59, USAF Academy, Colorado 80840, USA).

May 1–3, **Paraplegia Cure**, Palm Beach (National Paraplegia Foundation, 333 N. Michigan Avenue, Chicago, Illinois 60601, USA).

May 3–5, **Education and Training of Engineers**, Greenwich (Manager, IEE Conference Department, Savoy Place, London WC2R 0BL).

May 3–7, **Protides of the Biological Fluids**, Bruges (Colloquium on Protides of the Biological Fluids, Simon Stevin Instituut, Jerusalemstraat 34, Brugge, Belgium).

May 5, **Industrial Applications of Queueing Theory**, London (Manager, IEE Conference Department, Savoy Place, London WC2R 0BL).

May 6-7, **Interactions—Problems in the History and Philosophy of Science**, Enfield (Dr I. Grattan-Guinness, Enfield College of Technology, Queensway, Enfield, Middlesex).

May 6-11, **American Ceramic Society Meeting**, Washington DC (Sidney Diamond, School of Engineering, Purdue University, Lafayette, Indiana 47907, USA).

May 8-11, **Quantum Electronics**, Montreal (J. A. Armstrong, IBM Thomas J. Watson Research Center, PO Box 218, Yorktown Heights, New York 10598, USA).

May 9, **Crop Protection**, Ghent (Professor W. Welsaert, Faculteit Van de Landbouwwetenschappen, Coupure Links 533, B-9000 Ghent, Belgium).

May 9, **Cancer at the Crossroads and the Challenge for the Future**, London (Mr P. A. Sturgess, Marie Curie Memorial Foundation, 124 Sloane Street, London SW1X 9BP).

May 20, **Blast Transformation of Lymphocytes**, Poznan (Dr S. Mackiewicz, Organizing Committee, Department of Immunology, Medical School, Poznan, Szkolna 8/12, Poland).

May 22-24, **The Theory and Practice of LD Steelmaking**, Salford (Administrative Assistant (Short Courses), University of Salford, Salford M5 4WT).

May 22-26, **The Treatment of Digestive System Cancer**, Milan (Secretariat, c/o Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, 20133 Milano, Italy).

May 23-26, **European Teratology Society Conference**, Prague (Dr J. E. Purkyně, Czechoslovak Medical Society, Sokolská, Praha 2, Czechoslovakia).

May 24-26, **Photo-optical Applications in Security, Surveillance and Law Enforcement**, Chicago (Society of Photo-optical Instrumentation Engineers, National Offices, PO Box 288, Redondo Beach, California 90277, USA).

May 25-27, **Mechanisms and Regulation of Craniofacial Morphogenesis**, Nijmegen (Dr Frans Van der Linden, Department of Orthodontics, University of Nijmegen, "Heyendaal" Philips vandenlaan 25, Nijmegen, The Netherlands).

May 29-31, **Heat Transfer**, Winnipeg (R. E. Chant, Department of Mechanical Engineering, University of Manitoba, Winnipeg, Manitoba, Canada).

May 29-June 1, **Transplantation**, Lyon (Dr R. Triau, Institut Mérieux, 17 rue Bourgelat, Lyon II, France).

May 30, **The Detection and Relevance of Excited States in Photosynthesis and Vision**, London (Dr Frank Kaufman, The Royal Institution, 21 Albemarle Street, London W1X 4BS).

May 31-June 2, **Endotoxin**, Warrenton, Virginia (Endotoxin Conference, Chan-

ning Laboratory, Boston City Hospital, Boston, Massachusetts 02118, USA).

June 2-8, **Man, Air and Water**, Paris (L'Homme l'air et l'eau, 8 rue de la Michodière, 75 Paris 2, France).

June 5-7, **Canadian Chemical Conference and Exhibition**, Quebec (CIC, 151 Slater Street, Ottawa K1P 5H3, Canada).

June 5-8, **Combustion and Environment**, Sheffield (T. Chippindale, 2 Warwick Crescent, Harrogate HG2 8JA, Yorkshire).

June 5-9, **Spectrographic and Chromatographic Analysis Methods**, Paris (Secretariat of the GAMS, 10 rue du Delta, 75 Paris 9, France).

June 5-9, **Thermionic Electrical Power Generation**, Jülich (Dr P. von Handel, Kernforschungsanlage Jülich GmbH, D-5170 Jülich, Postfach 365, Federal Republic of Germany).

June 5-9, **Image Processing, Coding and Transmission**, Lafayette (Division of Conferences and Continuation Services, 116 Memorial Center, Purdue University Lafayette, Indiana 47907, USA).

June 5-9, **Organic Sulphur Chemistry**, Lund (Fifth Symposium on Organic Sulphur Chemistry, Chemical Center, Box 740, S-220 07 Lund 7, Sweden).

June 5-9, **The Stratigraphy, Structure and Evolution of the Northern Piedmont**, Frederick, Maryland (Dr G. W. Fisher, Department of Earth and Planetary Science, Johns Hopkins University, Baltimore, Maryland 21218, USA).

June 5-16, **Human Environment**, Stockholm (UN Conference on the Human Environment, Palais des Nations, 1211 Geneva, Switzerland).

June 6-7, **Stack Sampling**, Chicago (Mrs Nancy Nazarens, Walter C. McCrone Associates, 493 East 31st Street, Chicago, Illinois 60616, USA).

June 6-8, **Frequency Control**, Atlantic City (Commanding General, US Army Electronics Command, Attention AMSEL-TL-SF (Mr J. M. Stanley), Fort Monmouth, New Jersey 07703, USA).

June 6-9, **Animal Reproduction and Artificial Insemination**, Munich (Congress Secretary, 53 Bonn 1, Adenauerallee 176, Germany).

June 8-9, **The Structure and Formation of Eukaryotic Ribosomes**, Glasgow (Professor H. M. Keir, The Biochemical Society, 7 Warwick Court, High Holborn, London WC1R 5DP).

June 8-9, **Cellular Modification and Genetic Transformation by Exogenous Nucleic Acids**, Baltimore (Dr C. J. O'Donovan, Miles Laboratories Inc., Elkhart, Indiana 46514, USA).

Reports and Publications

not included in the Monthly Books Supplement

Great Britain and Ireland

Printing and Publishing Industry Training Board. Training Recommendation 6: Editorial Staff in Periodicals. Pp. 23. (London: PPITB, 1972.) 30p.

The Independent University at Buckingham—Progress Report, January 1972. Pp. 9. (London: The Independent University at Buckingham, 2 Lord North Street, 1972.)

Department of Education and Science. Central Arrangements for promoting Education Technology in the United Kingdom. (Report of the Working Party appointed by the Secretary of State for Education and Science.) Pp. viii+48. (London: HMSO, 1972.) 37p.

Mental Health Research Fund. Annual Report and Accounts 1971. Pp. 18. (London: Mental Health Research Fund, 1972.)

International Computers (Holdings) Limited. Annual Report and Accounts 1971. Pp. 28. (London, SW15: International Computers (Holdings) Limited, 1972.)

Building Research Station Digest, No. 138: Operating Costs of Services in Office Buildings. Pp. 4. (London: HMSO, 1972.) 5p.

Ministry of Agriculture, Fisheries and Food. Agricultural Chemicals Approval Scheme. 1972 List of Approved Products and their Uses for Farmers and Growers. Pp. 168. (London: Ministry of Agriculture, Fisheries and Food, 1972.)

Cambridge University Reporter, Vol. CII, Special No. 9: Annual Report of the Board of Graduate Studies for 1970. Pp. 96. (Cambridge: Secretary of the Board of Graduate Studies, The University, 1972.) 4p.

British Pharmacological Society Handbook 1972. Pp. 56. (London: British Pharmacological Society, c/o Professor J. R. Vane, Royal College of Surgeons of England, 1972.)

Universities Research Reactor—Annual Report 1970/1971. Pp. 27. (Risley, Warrington: Universities Research Reactor, 1972.)

A Year of Action. By President Nixon. (State of the Union 1972.) Pp. 14. (London: US Information Service, 1972.)

Oxford Study Groups with Industry, 1968-1971. (Progress Report on Applications of Differential Equations, Mathematical Institute, Oxford.) Pp. 12. (London: Science Research Council; Oxford: The University, 1972.)

Philosophical Transactions of the Royal Society of London. A: Mathematical and Physical Sciences. Vol. 271, No. 1216 (3 February 1972): Dynamo Action of Fluid Motions with Two-Dimensional Periodicity. By G. O. Roberts. Pp. 411-454. (London: The Royal Society, 1972.) £1.15; \$3.

Department of Education and Science. Children with Specific Reading Difficulties: Report of the Advisory Committee on Handicapped Children. Pp. iii+8. (London: HMSO, 1972.) 16p net.

Biology and the Soul. By Professor John Hick. (The Twenty-Fifth Arthur Stanley Eddington Memorial Lecture delivered at Cambridge University, 1 February 1972.) Pp. 29. (London: Cambridge University Press, 1972.) 30p; 95 cents (USA).

Building Research Station. Digest 110: Condensation. Pp. 8. 5p. Digest 138: Operating Costs of Services in Office Buildings. Pp. 4. 5p. (London: HMSO, 1972.)

Young Fabian Pamphlet No. 29: Swedish Social Democracy. Into the Seventies. By Russell Lansbury. Pp. 24. (London: The Fabian Society, 1972.) 25p.

Bulletin of the British Museum (Natural History). Zoology, Vol. 21, No. 8: Miscellanea. Pp. 285-361. (London: British Museum (Natural History), 1972.) £2.60.

Natural Environment Research Council—Institute of Geological Sciences. British Regional Geology. Northern England. Fourth edition. By B. J. Taylor et al. Pp. x+121+13 plates. (London: HMSO, 1971.) 40p net.

The Zoological Record, 1967, Vol. 104, Section 13: Insecta. Prepared by the Staff of the Zoological Society of London. Pp. xv+704. (London: The Zoological Society of London, 1971.) £12; \$29.

Industry, Science and Universities—Appendix 1: Replies from Industry. Industry, Science and Universities—Appendix 2: Replies from Universities. (Appendix to the Report of the Working Party on Universities and Industrial Research to the Universities and Industry Joint Committee.) (London: Confederation of British Industry, 1971 and 1972.) Appendix 1 £4; Appendix 2 £6.

Proceedings of the Royal Irish Academy. Vol. 72, Section B, Nos. 1, 2, 3: Utilisation of Peat—1. Methods of Obtaining Fermentable Substrates. Utilisation of Peat—2. Preliminary Investigations on Factors Influencing Small Scale Production of *Candida utilis*. Utilisation of Peat—3. A Study of Acid Catalysed Peat Extract. By A. J. McLoughlin and E. Küster. Pp. 1-24. 30p. Vol. 72, Section B, No. 4: Stratigraphy and Sedimentology of the Lower Palaeozoic Greywacke Formations in Counties Kildare and West Wicklow. By P. M. Brück. Pp. 25-54+plates 1-3. 57p. Vol. 72, Section B, No. 5: Anaerobic Glycolysis in Biopsy and Post-Mortem Porcine *Longissimus dorsi* Muscle. By P. J. V. Tarrant, J. V. McLoughlin and M. G. Harrington. Pp. 55-73. 28p. (Dublin: Royal Irish Academy, 1972.)

- Department of Education and Science. Education Survey No. 14: The Continuing Needs of Immigrants. Pp. 34. (London: HMSO, 1972.) 30p net. [92]
- Science Policy, Vol. 1, No. 1, January/February 1972. (London: Science Policy Foundation, 1972.) [92]
- Tate and Lyle, Ltd. Group Research and Development—Annual Report 1971. Pp. 68. (Keston, Kent: Tate and Lyle Limited, 1972.) [92]
- The Commonwealth Foundation. Occasional Paper No. 13: The Role of the Professions in a Changing World. (Report on a Conference held at the Professional Centre of Singapore, October 1971.) Pp. 96. (London: The Commonwealth Foundation, Marlborough House, 1971.) [102]
- Medical Research Council. Handbook 1971–1972. Pp. iv+250. (London: Medical Research Council, 1971.) [112]
- Education and Research Yearbook 1972. Edited by I. A. Haycraft. Pp. xii+305. (London: Operational Research Society, 1972.) [112]

Other Countries

- US Department of the Interior: Geological Survey. Professional Paper 599-G: Lunar Terrain Mapping and Relative-Roughness Analysis. By Lawrence C. Rowan, John F. McCauler and Esther A. Holm. Pp. iv+32, 45 cents. Professional Paper 694: Sulfide Minerals in the G and H Chromitite Zones of the Stillwater Complex, Montana. By Norman J. Page. Pp. iii+20, 35 cents. (Washington, DC: Government Printing Office, 1971.) [31]
- Sick Fund of the General Federation of Labour in Israel, Kupat-Holim—Year Book, Vol. 1. Pp. 227. (Kupat-Holim: Sick Fund of the General Federation of Labour, 1971.) [12]
- OECD. The Problems of Persistent Chemicals: Implications of Pesticides and other Chemicals in the Environment. (Report of the Study Group on Unintended Occurrence of Pesticides.) Pp. 113. (Paris: OECD; London: HMSO, 1972.) 12 francs; 92p. [12]
- Instituto Mexicano de Recursos Naturales Renovables. Mesas Redondas sobre Deterioración del Ambiente. (Auditorio del Instituto Mexicano de Recursos Naturales Renovables, 21 a 25 de Junio de 1971. Aportación para la Comisión Preparatoria de México a la Conferencia de las Naciones Unidas sobre el Medio Humano, Estocolmo, 1972.) Pp. x+258. (Mexico, D.F.: Ediciones del Instituto Mexicano de Recursos Naturales Renovables, A.C., 1971.) [22]
- Koninklijk Nederlands Meteorologisch Instituut, De Bilt. Marine Climatological Summaries for the Mediterranean and Southern Indian Ocean, Vol. 4, 1964. Pp. xi+360. (De Bilt: Koninklijk Nederlands Meteorologisch Instituut, 1972.) 25 fl. [22]
- Department of Energy, Mines and Resources. Ottawa. Annual Report 1969/1970. Pp. 81. (Ottawa: Information Canada, 1971.) [22]
- Canada: Department of Energy, Mines and Resources. Geological Survey of Canada. Memoir 363: Geology of Bonaparte Lake Map-Area, British Columbia. By R. B. Campbell and H. W. Tipper. Pp. 100, \$450. Paper 70-48: Geological Comparison Between East European and Canadian Uranium Deposits. By V. Ruzicka. Pp. ix+196 (7 plates). \$5. Paper 71-24: Paleomagnetic Notes on Some Minor Tertiary Igneous Bodies, Vancouver, British Columbia. Paleomagnetic Notes on the Karmutsen Basalts, Vancouver Island, British Columbia. By D. T. A. Symons. Pp. iii+25, \$1.50. Paper 72-1: Report of Activities, Part A: April to October, 1971. Pp. ix+243, \$2. (Ottawa: Information Canada, 1971 and 1972.) [22]

- Annals of the South African Museum. Vol. 57, Part 11: *Centrophorus squamosus* (Bonnaterre) (Chondrichthyes, Squalidae) in the Eastern South Atlantic. By P. A. Hulley. Pp. 265–270, R0.80. Vol. 57, Part 12: The Genus *Gennadas* in the Waters Around Southern Africa. By Brian Kensley. Pp. 271–294, R2.00. Vol. 59, Part 1: The New Skulls of *Parapapio antiquus* from Taung and a Suggested Phylogenetic Arrangement of the Genus *Parapapio*. By Wolfgang Maier. Pp. 1–16+1 plate, R1.80. Vol. 59, Part 2: The Early Therapsids. By L. D. Boonstra. Pp. 17–46, R3.30. (Cape Town: South African Museum, 1971.) [22]
- South African Sugar Association. Experiment Station, Mount Edgecombe—Annual Report 1970/1971. Pp. 48. (Mount Edgecombe: South African Sugar Association, 1972.) [22]
- US Department of the Interior: Geological Survey. Water-Supply Paper 1907: Surface Water Supply of the United States 1961–65. Part 3: Ohio River Basin. Vol. 1: Ohio River Basin Above Kanawha River. Pp. ix+621. (Washington, DC: Government Printing Office, 1971.) \$3.25. [72]
- Munger Africana Library Notes. Issue No. 7: An Exploration Near Afades and Timbuktu in Advance of the 1973 Total Solar Eclipse. By Jan M. Paschoff. Pp. 52, \$2. Issue No. 9: Aggression and Violence in Man. A Dialogue between Dr. Louis Leakey and Mr. Robert Ardrey. Pp. 24, \$3. (Pasadena, California: The Munger Africana Library, California Institute of Technology, 1971.) [72]
- Deutsche Akademie der Wissenschaften zu Berlin. Forschungsbereich Kosmische Physik. Veröffentlichungen des Zentralinstituts Physik der Erde. Nr. 8: Die Bestimmung des Richtungsvektors Riva-Sofia aus Beobachtungen des Satelliten "Echo 2". Von K. Arnold et al. Pp. 60, Nr. 10: Absolute Schweremessungen mit Reversionspendeln in Potsdam 1968–1969. Von R. Schüler et al. Pp. 193. Nr. 11: Analyse der Beobachtungsergebnisse der Astronomisch-geodätischen Langenbestimmung Borowiec-Dresden-Potsdam aus dem Jahre 1966. Von J. Höpfner. Pp. 123. (Potsdam: Deutsche Akademie der Wissenschaften zu Berlin, 1971.) [72]
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- The Nucleus: Annual Review of the Science Foundation for Physics and the School of Physics within the University of Sydney. Pp. 84. (Sydney: Science Foundation for Physics and the School of Physics within the University of Sydney, 1972.) [82]
- Higher Education, Vol. 1, No. 1 (February 1972). Pp. 1–140. Published quarterly. Subscription rates for volume 1: Individuals who warrant the journal is for their own personal use, Dfl. 40.00 including postage; Libraries, Research Institutions and others, Dfl. 70.00 plus Dfl. 7.00 postage. (Amsterdam: Elsevier Publishing Company, 1972.) [102]
- United States Department of the Interior: Geological Survey. Professional Paper 676: Geology and Fuel Resources of the Fruitland Formation and Kirtland Shale of the San Juan Basin, New Mexico and Colorado. By James E. Fassett and Jim S. Hinds. Pp. iv+76+3 plates. Water-Supply Paper 1936: Surface Water Supply of the United States 1961–65. Part 15: Alaska. Pp. vii+342+1 plate. (Washington, DC: Government Printing Office, 1971.) [112]
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- Australia: Commonwealth Scientific and Industrial Research Organization. Division of Chemical Engineering—Biennial Report 1969/1971. Pp. 33. (Clayton, Victoria: CSIRO, 1972.) [142]

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- Fisheries Research Board of Canada. Bulletin 176: A Synopsis of Canadian Marine Zooplankton. By C. T. Shih, A. J. C. Figueira and E. H. Grainger. Pp. 264. (Ottawa: Information Canada, 1971.) \$5. [142]
- Institut Royal Météorologique. Publications, Série A, No. 74: La Pollution Atmosphérique par les Oxydes de Soufre et la Fumée dans les Agglomérations de Charleroi et Anvers au Cours de la Période du 1er Avril 1968 au 31 Mars 1969. Par J. Bouquiaux, J. Grandjean et M. Legrand. Pp. 32. (Bruxelles: Institut Royal Météorologique, 1971.) [142]
- Australia: Commonwealth Scientific and Industrial Research Organization. Annual Report of the Division of Tribophysics, 1970/1971. Pp. 32. (Melbourne: CSIRO, 1971.) [142]
- World Health Organization. Technical Report Series, No. 485: Human Development and Public Health—Report of a WHO Scientific Group. Pp. 40. (Geneva: WHO; London: HMSO, 1972.) 4 Sw. francs; 40p; \$1. [152]
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- National Museums of Canada. Publications in Biological Oceanography, No. 3: The Marine Molluscs of Arctic Canada. By Elizabeth Macpherson. Pp. vii+149, \$3.50. Publications in Folk Culture, No. 2: A Garland of Rue—Lithuanian Folksongs of Love and Betrothal. Collected and edited by Kenneth Peacock. Pp. viii+60, \$2.50. Anthropological Series No. 87: Contributions to Anthropology, VII: Archaeology and Physical Anthropology. A collection of five papers by J. V. Wright, R. S. Kidd, Roscoe Wilmet, Ruth Gruhn and Robert McGhee. Pp. viii+191 (9 plates). \$3. Publications in Folk Culture No. 1: Folksongs from Southern New Brunswick. Collected and edited by Helen Creighton. Musical transcriptions by Kenneth Peacock. Pp. x+238, \$4.25. (Ottawa: National Museums of Canada, 1971.) [152]
- US Department of the Interior: Geological Survey. Professional Paper 656: Investigations of Ferruginous Bauxite and Other Mineral Resources on Kauai and a Reconnaissance of Ferruginous Bauxite Deposits on Maui, Hawaii. By S. H. Patterson. Pp. v+74+11 plates. (Washington, DC: Government Printing Office, 1971.) [152]
- Canada: Department of Energy, Mines and Resources. Geological Survey of Canada. Paper 71-40: Computer-Based Storage and Retrieval of Geoscience Information: Bibliography 1946–69. By J. Hruska and C. F. Burk, Jr. Pp. v+52. (Ottawa: Information Canada, 1971.) \$1.50. [152]
- Carnegie Institution. Annual Report of the Director of the Department of Terrestrial Magnetism, 1970/1971. (Reprinted from *Carnegie Institution Year Book 70*, for the year July 1, 1970–June 30, 1971.) Pp. 323–388. (Washington, DC: Carnegie Institution, 1971.) [162]
- Smithsonian Contributions to Zoology, No. 109: Partial Revision of the Genus *Sthenelais* Kimberg (Polychaeta: Sigalionidae) with Diagnoses of Two New Genera. By Marian H. Pettibone. Pp. 40, 50 cents. No. 111: Systematic Notes on a Collection of Birds from Kenya. By S. Dillon Ripley and Gorman M. Bond. Pp. 21, 35 cents. (Washington, DC: Smithsonian Institution Press, 1971. For sale by US Government Printing Office, Washington.) [162]

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